The Pharmacology of LSD

A Critical Review

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Contents

1 Introduction *1*

Discovery of LSD *2*

LSD as a psychotomimetic *4*

LSD and the military *5*

LSD as a psychotherapeutic tool *7*

LSD as a psychedelic *9*

Research restrictions and recent applications *11*

2 Pharmacological effects *13*

Summarized overview *13*

Chemistry *14*

Pharmacokinetics *21*

Pharmacodynamics *33*

Pharmacological and toxicological effects *51*

Neurophysiological effects *59*

Tolerance and Cross-tolerance *81*

3 Interactions of LSD *93*

Interaction with endogenous substances *93*

Interactions with exogenous substances *98*

4 Psychological effects *129*

Visual phenomena *130*

Acoustic phenomena *130*

Tactile phenomena *131*

Changes in body perception *131*

Synaesthesias *132*

Hypersuggestibility *132*

Changes in spatial and temporal perception *132*

Thought disorders *132*

Decoupling of perception and conceptual cognition *133*
Changes of affectivity *133*
Alterations of consciousness and ego functions *134*
Hypermnesias *135*
Mysticomimetic effects *135*

5 Neuropsychological effects *137*
Attention and concentration *137*
Abstract thinking *139*
Intellectual functions *141*
Psycho- and visuo-motoric abilities *143*
Judgement of time *144*
Estimation of weight, size, and spatial relations *144*

6 Effects of LSD on psychiatric patients *147*
Effects in schizophrenics *147*
Effects in autistic children *148*
Effects in other mental disorders *148*
Effects on blood-relatives of schizophrenics *149*
Effects in patients with epilepsy *149*

7 Long-term and untoward effects of LSD use *151*
Psychological long-term effects *151*
Surveys on risks of experimental and psychotherapeutic use *152*
Untoward and adverse effects *153*
Flashbacks as after-effects *155*
Indications of permanent changes to the CNS? *155*
Dependence *156*

References *159*

Author Index *205*

Subject Index *209*

Chapter 1

Introduction

When we started working on this book, we sought an overview of the pharmacology of LSD, the world's most commonly used hallucinogenic or psychedelic substance of the past decades. Astonishingly, such a study was not available.

This omission may well have its origins in the confusing variety of studies, and their difficult bibliographic availability. Beyond question, the increase in the worldwide use of this central psychedelic substance has created an enormous thirst for information regarding its physiological and emotional effects, how it works, its interaction with other substances, its possible positive effects, and its potential side effects and complications.

By 1971, research using hallucinogens on humans practically came to a stop as a result of political pressure consequent to the increasing spread of illegal, uncontrolled consumption from the middle of the 1960s. Since then, illegal consumption has in no way diminished; rather, it has continued at the same level since the beginning of the 1970s and at least into the 1990s (Henderson & Glass, 1994). At present, in North America alone, the number of people who have used hallucinogens is estimated to be 23.5 million, of which by far the largest number used LSD (SAMSHA, 2007). Reports on spectacular, abnormal behaviour and other complications from uncontrolled consumption of LSD, by contrast, have decreased to the point where they are almost invisible (Prepeliczay, 2002). This is largely due to a kind of cultural assimilation and informal social controls, in the sense of a 'professionalization' in the usage of the substance in the relevant subcultures (Rätsch, undated). However, in medical science, there is still a great deficit of information on the substance's complete pharmacological profile, as can be easily ascertained from the relevant publications, such as reference books on addiction or general articles (Pletscher & Ladewig, 1994; Abraham *et al.*, 1996). Imprecise or even false information is the norm, rather than factually correct and complete statements. Earlier overviews are given by Osmond (1957), Hoffer and Osmond (1967) the anthology of Siva Sankar (1975) and a few short reviews (Hollister 1968a, 1974; Rubin 1957; Giarman 1967).

Despite a break in research of many years, scientific interest has apparently not waned, as proved by two current pilot studies administering LSD to human subjects, and by two large international conferences on the subject (Pletscher & Ladewig, 1994 and the International Congress LSD—Problem Child and Wonder Drug, Basel, Switzerland, 2006). In addition, two recent volumes about the therapeutic effects of psychedelic drugs have appeared (Winkelman & Roberts, 2007; Jungaberle *et al.*, 2008).

It is also noteworthy that during the 1980s and 1990s a lot of new potential neuroleptic compounds were tested on LSD-trained animals during drug-discrimination studies. This eventually lead to the development of some major 'second generation' neuroleptics such as risperidone (Meert *et al.*, 1989, 1990; Colpaert, 2003).

Discovery of LSD

Since the beginning of the twentieth century, the pharmacological effects of diverse plants have been investigated in relation to their suitability as medicines. Firstly, their effects as a whole plant were investigated, then the effects of the isolated chemical components, and finally the effects of synthetically produced chemical derivatives of these chemical parts on animals and, if necessary, on humans. In this context the studies by the Swiss chemist for natural products, Dr Albert Hofmann, were done on the identification and chemistry of the ergot alkaloids (derived from the sclerotia of the filamentous fungus *Claviceps purpurea*, cf. Figure 1.1) for the Sandoz Company (Basel, Switzerland), during the 1930s (Hofmann, 1964). The investigation of ergot alkaloids had been a main field of research of the Sandoz laboratories since the discovery of ergotamine by Artur Stoll in 1918. It was and still is used for childbirth bleeding and migraine. The intention was to find new medicines, which could

Fig. 1.1 Ergot sclerotia growing from rye.

be made from these poisonous alkaloids, using purification and chemical manipulation.

We know that in the Middle Ages there were poison epidemics when ergot fungus (usually growing on rye) was accidentally included in bread. Two types of ergotism have been recognized: *gangrenous* and *convulsive*. The former is characterized by dry gangrene of the extremities and is often accompanied by vivid visual hallucinations. Visions of devils and flames experienced by its victims led to the diagnosis of 'St Anthony's fire' and 'holy fire'. Symptoms of convulsive ergotism include distorted sensory perception, delirium, psychosis, hallucination, and painful muscular contractions that lead to convulsions (Barger, 1931). Ergot was also known to be used in obstetrics and for headaches (Hamburger, 1848).

Starting from lysergic acid, the active principle and foundation stone of the ergot alkaloids, Hofmann succeeded in developing a number of highly effective new medicines from the ergot fungus. Some of these are still in use today for bleeding after childbirth (Methergine®) and for the enhancement of cerebral circulation in geriatric patients (Hydergine® and Dihydergot®) (cf. Sandoz AG, undated). Sandoz was able to make large profits from the sales of these medicines. LSD, by contrast, became popular outside the scientific, medical world, and was produced on a world-wide scale, but sold without any licence fees.

LSD was first synthesized during the course of investigations on semi-synthetic amides of lysergic acid, after *d*-lysergic acid L-propanolamide was found to be identical with the natural alkaloid ergometrine (ergonovine). In 1938, as the twenty-fifth product (hence the name LSD-25) in a synthesizing sequence, Hofmann made another half-synthetic derivative of lysergic acid, lysergic acid diethylamide (Stoll & Hofmann, 1943). Hofmann synthesized this compound with the intention of creating a circulation and breathing stimulant, because of its structural similarities with nicotinic acid diethylamide (Coramin®), a known analeptic. Synthesized in 1938, LSD-25 was found to have strong uterotonic effects (about 70% that of ergobasine) and caused restlessness in laboratory animals. However, no obvious benefits were noted, and it was shelved—which usually consigned a research substance to permanent oblivion (Hofmann, 1979, 1983).

However, a new synthesis of the substance did, after all, occur, as Hofmann here describes:

> A peculiar presentiment that this substance could possess other effective qualities than those found in the first test, led me to undertake another synthesis of LSD-25 five years later, in order to pass it on once again to the pharmacological department for extended testing … In the spring of 1943, I then repeated the synthesis of LSD-25.
>
> (Hofmann, 1979, p. 57)

> In the final step of the synthesis, during the purification and crystallization of lysergic acid diethylamide in the form of a tartrate (from tartaric acid salt), I was interrupted in my work by unusual sensations. I take the description of this incident from the report that I sent at that time to Professor Stoll: Last Friday, April 16, 1943, I was forced to interrupt my work in the laboratory in the middle of the afternoon and proceed home, as I was seized by a remarkable restlessness, combined with a slight dizziness. At home I lay down and sank into a not-unpleasant intoxicated-like condition that was characterized by extremely stimulated imagination. In a dream-like state, with eyes closed (I found the daylight to be unpleasantly glaring), an uninterrupted stream of fantastic pictures of extraordinary plasticity with intense, kaleidoscope-like play of colors surged in on me. After some 2 hours this condition faded away.
>
> (Hofmann, 1979, p. 58)

In order to follow up his suspicion that this exotic experience was related to the work on LSD, Hofmann undertook a self-experiment a few days later with 250 μg of LSD. The changes he then experienced were much more disturbing, but similar to those he had experienced in the first, involuntary absorption of the substance. Thus, the cause of the strange, inebriated condition was explained. During the following years, Stoll (1947) researched the effect of LSD on volunteers and found profound changes in subjective experience (e.g. intensification of affectivity, illusions and pseudo-hallucinations, as well as alterations of thinking and associations), which cannot really be said to be 'psychotic'. He also found hypermnestic re-living of long-forgotten or repressed memories, synchronized with the appropriate emotions.

It should be mentioned that Hofmann later found natural lysergic acid derivates related to LSD in the search for the active constituents of the Aztec magic plant Ololiuqui *(Rivea corymbosa)* (Hofmann & Tscherter, 1960).

LSD as a psychotomimetic

In 1947, Sandoz began distributing LSD to researchers worldwide under the trademark Delysid®. Experimentally, Sandoz recommended self-administration of the drug by psychiatrists, so that they could gain an understanding of the subjective experience of psychotic patients. Psychotherapeutically, they suggested that LSD could release repressed thoughts and feelings in neurotic patients.

At that time, the working hypothesis was that LSD and similar hallucinogens induced psychotic conditions, which were called 'model psychoses' (a term coined by German mescaline researcher, Kurt Beringer in 1927). It was also around that time that psychiatry became aware of a possible aetiology of psychotic illnesses by an aberration of the complex biochemistry of the brain's neurotransmitters (Green, 2008). LSD supplied an evident clue for this in its effectiveness in extremely small doses. Researchers tried to determine the

mechanism by which LSD exerted its effects, and examined whether the same pathways were affected in schizophrenics. Thus, in the following two decades, a great many biochemical, physiological, and psychological experiments involving LSD were carried out on animal and human subjects. The number of scientific publications on LSD in the years from 1943 to 1970 almost reached the 10,000 mark. This resulted in LSD being talked about as 'the most intensively researched pharmacological substance ever'.

Although a few researchers concluded that symptoms of LSD intoxication and schizophrenia were fundamentally indistinguishable, since the mid-1950s the belief that LSD produces a reasonable model psychosis has declined (Langs and Barr, 1968). The consensus was stated well by the prominent Swiss psychiatrist Manfred Bleuler (1959).

1. Schizophrenia cannot be characterized by the presence of any particular isolated symptom. Only the *combination* of symptoms (such as thought disorders, ego-disturbances, depersonalization, and hallucinations), progressing gradually to render the individual incapable of controlling his or her life, is characteristic of schizophrenia.
2. The psychopathological pictures induced by LSD do not correspond to those of schizophrenia (for example visual phenomena are markedly dominant with LSD, acoustic hallucinations are dominant in schizophrenia).
3. The alienating and dissonant, unharmonious sensations, the *Uneinfühlbare*, typical in schizophrenia, are missing with LSD.
4. Schizophrenics can easily discriminate between toxic and original psychotic phenomena.

These insights marked the end of the era of LSD as a psychotomimetic. But this line of research was later followed by recent neuro-imaging research with some hallucinogens (Hermle *et al.*, 1992, 1996; Vollenweider *et al.*, 1997, Vollenweider *et al.*, 1998; Gouzoulis-Mayfrank, 1999; Riba *et al.*, 2006) to elucidate neurophysiological pathways and patterns of psychotic states.

During the 1950s and 1960s, LSD research was being conducted at about 40 major American, Canadian, and European medical centres (Table 1.1). Research on LSD and other hallucinogens was very broad in the 1950s and 1960s, and had numerous scientific facets (Figure 1.2).

LSD and the military

In 1953, the Central Intelligence Agency (CIA) entered the scene, secretly funding LSD research at major American universities. Only a few researchers were aware of this CIA funding of their research.

Table 1.1 Decades of research on LSD

Year	Events
1943–1950	Discovery, chemical description, and characterization of psychological and physiological effects.
1950–1960	Research on metabolism, pharmacokinetics, pharmacodynamics, tolerance, cross-tolerances, cognitive, psychopathological, and biochemical effects. Studies with antagonists and derivatives of LSD. Psychochemical warfare research. Psychotherapy research began in 1955.
1960–1970	Further research on psychological effects. Establishment and dissemination of usage in psychotherapy (psycholytic and psychedelic therapy). Since 1963, spread and use outside of the medical framework. 1966 was the year that adversely changed LSD's image.
1970–1980	Spread of sub-cultural use. Investigation of long-term effects under controlled conditions, as well as with psychedelic therapy. Studies on complications and consequences of uncontrolled use and interactions of LSD with other substances. Strict limitations on human research. Halt of its use in psychotherapy and human research in 1973.*
1980–1990	Large decrease in complications through increase in competence by the recreational users of LSD. LSD derivatives as tracers in the study of neurotransmitters in animals.
1990 to present	Since 1990, re-popularization of LSD in the setting of the Rave Culture youth movement. A study in 1991 stated that more LSD was consumed worldwide in 1991 than had been consumed in 1970. There has also been a clear reduction in common dosage (from 200–300 μg to 50–100 μg). This implies usage mainly as a stimulant, often in combination with MDMA (a.k.a. 'Ecstasy'). Since 1988, renewed interest in the use of LSD in psychotherapy. In 2007, approvals for the first neuro-scientific study with human subjects, and a study treating anxiety in life-threatening illnesses.

* Exceptions: Prof. Leuner (Germany) up to 1986; Czech psychotherapy research up to 1978; and treatment of terminal cancer patients at Spring Grove Hospital (Maryland, USA) up to 1985.

The CIA was searching for a truth-drug for interrogating suspected Communist spies, and a chemical-warfare agent to incapacitate troops and to manipulate behaviour of its own and foreign agents (Scheflin & Opton, 1978; Marks, 1979). CIA directors wrote that they were interested in creating 'operationally pertinent materials along the following lines: a. Disturbance of memory; b. Discrediting by aberrant behaviour; c. Alteration of sex patterns; d. Eliciting of information; e. Suggestibility; f. Creation of dependence' (CIA memorandum to Harold Abramson, cited by Stevens, 1987, p. 81). The US Army gave LSD to 4,826 soldier volunteers between 1955 and 1975 (Novak 1997, p. 90). After more than 10 years of testing, the British and US military came to the

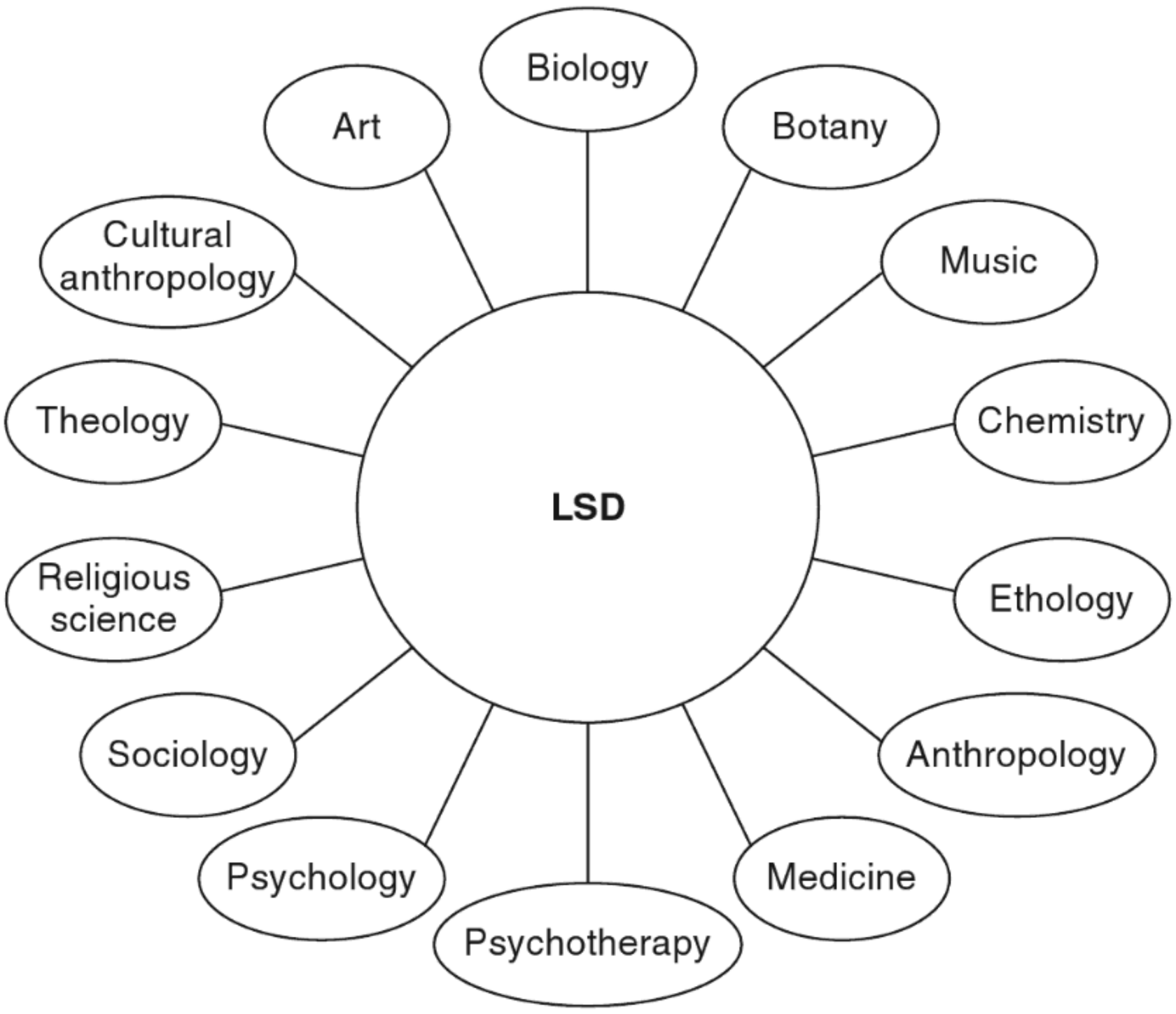

Fig. 1.2 Sciences involved in the study of LSD and other hallucinogens.

conclusion that the effects of LSD were not predictable, and that no two doses would guarantee a consistent result. 'From a tactical point of view, using LSD as a weapon would be analogous to using a gun that refused to be accurately aimed, worked intermittently, and fired different calibre shells in all directions' (Roberts, 2008, p. 49). At the beginning of the 1970s, nearly all military LSD testing came to a halt (Ketchum, 2006).

As may be recognized by future historians of science, the CIA-sponsored LSD research (as well as LSD research in general) made a major contribution to the paradigm shift in American psychology. By strongly supporting academic LSD research, the CIA transformed American psychology from behaviourism to more comprehensive (consciousness-including) approaches for understanding human behaviour and psychological functioning.

LSD as a psychotherapeutic tool

At the beginning of the 1960s, after the physiological harmlessness of the substance had been proved, the medical world expected its application as an aid in psychotherapy. Initial claims that LSD might damage human chromosomes did not stand up to a meticulous scientific examination (see Grof, 1980, for review).

LSD can induce a temporary dream-like change in consciousness. It increases the capability for introspection, activates affectivity, and alters mental association patterns as well as sensory experiences (e.g. mental imagery and pseudo-hallucinations). Through these factors and in an appropriately controlled setting, LSD may open up even treatment-resistant patients for insight-oriented psychodynamic psychotherapy (Grof, 1967; Leuner, 1983). This appeared to be a promising means of quickening an otherwise very time-consuming psychotherapeutic process (Abramson, 1967; Leuner, 1981, see Figure 1.3).

Two main methods of working with LSD in psychotherapy were established (cf. Grof, 1980; Leuner, 1981). The foundation for using LSD in *psycholytic therapy* had been laid by the end of the 1950s by European medical psychotherapists (above all, Sandison in England and Leuner in Germany). Psycholytic therapy used small doses (50–100 μg) in a series of low-dose sessions to facilitate psychoanalytic psychotherapy. *Psychedelic therapy* was developed by American researchers and therapists and involved administering large doses (250–500 μg) once or a few times. The resulting experiences of altered consciousness and/or mystical experiences, which may have given new insights and frames of reference, were emphasized. These experiences were even shown to alter personality traits of patients suffering from alcoholism and major personality disorders (Sherwood *et al*., 1962; Pahnke *et al*., 1970; Metzner, 1998).

The evaluations carried out showed promising results, so that the method spread quickly, and diverse scientific conferences were held on it (cf. Passie, 1997).

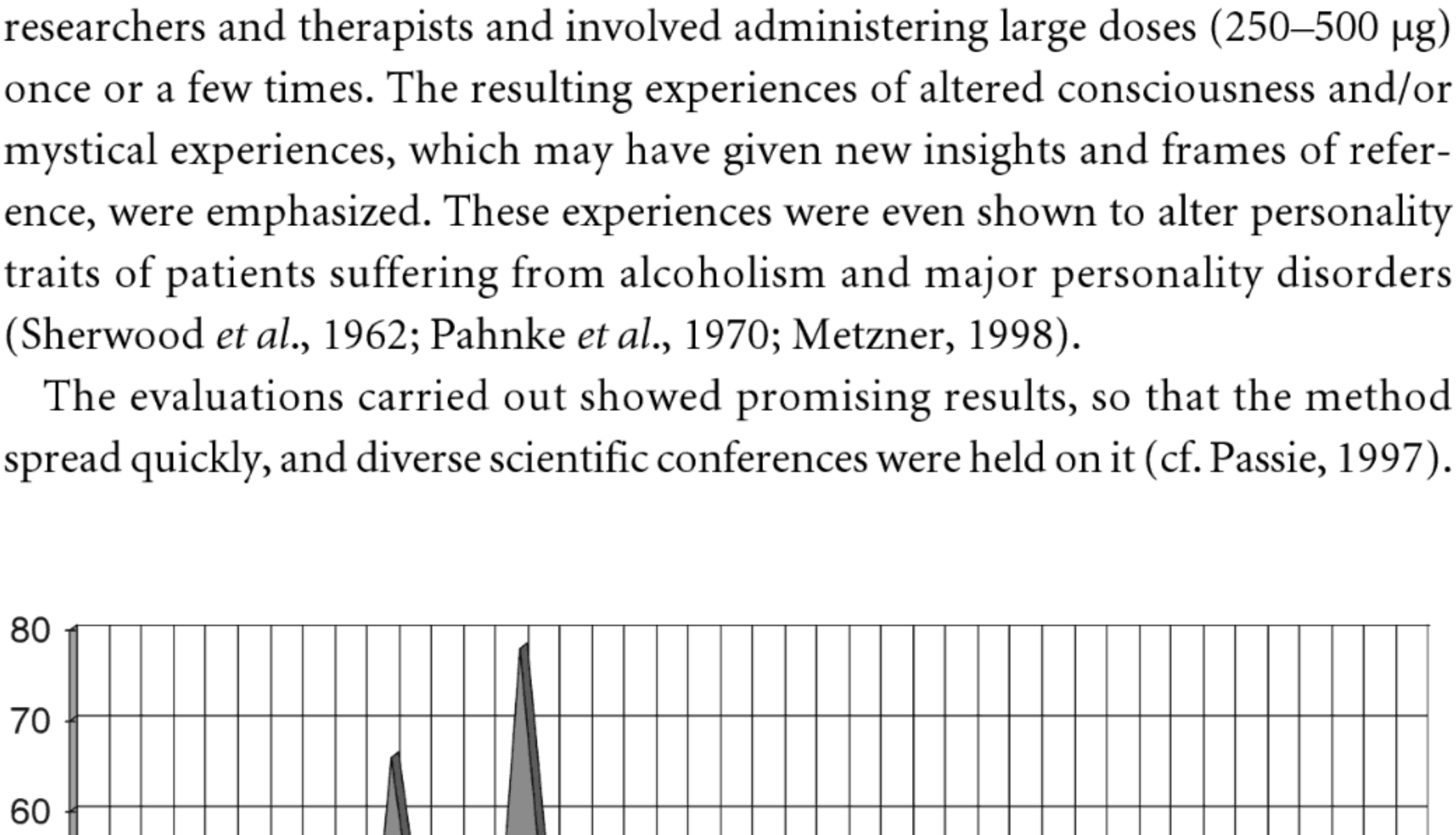

Fig. 1.3 Number of scientific publications on hallucinogen-assisted psychotherapy. Year of prohibition was 1967 (from Passie, 1997).

Although these therapeutic applications were stopped by the official backlash against the widespread use by laymen since the mid-1960s, some important heuristic models for understanding the deeper layers of the human psyche emerged from this research (Leuner, 1962; Masters & Houston, 1966; Grof, 1975). Of special note was the work of Stanislav Grof, who had a lasting influence and contributed to the forming of the 'fourth force in psychology', transpersonal psychology (Boorstein, 1980).

Due to the fact that no relevant risks could be ascertained in the psychotherapeutic and experimental use of LSD, as demonstrated by comprehensive retrospective surveys (Cohen, 1960; Malleson, 1971), Leuner was, uniquely, allowed to retain his special permit for use of hallucinogens until his retirement from Göttingen University in 1986.

LSD as a psychedelic

One of the most important scientific LSD researchers of the 1950s and 1960s, Sidney Cohen, M.D. (later head of the National Institute for Mental Health's (NIMH's) Division of Narcotics and Drug Abuse), may be looked at as the main discoverer of LSD as a 'psychedelic' drug. He expected to feel catatonic or paranoid during his self-experiment in 1955, but instead was taken by surprise: 'This was no confused, disoriented delirium, but something quite different.' His subsequent report described feeling an elevated peacefulness, as if 'the problems and strivings, the worries and frustrations of everyday life vanished; in their place was a majestic, sunlit, heavenly inner quietude … I seemed to have finally arrived at the contemplation of eternal truth' (Cohen in Abramson, 1960, p. 11). After this experience, Cohen immediately started his own LSD experiments to find out more about the core features of the LSD-induced state. However, after years of comprehensive experimentation, he concluded at a 1959 conference: 'Though we have been using the available measuring experiments, the check lists, the performance tests, the psychological batteries, and so forth, the core of the LSD situation remains in the dark, quite untouched by our activities' (Cohen in Abramson, 1960, p. 11). Hoping for more articulate reports, he turned to Gerald Heard, an expatriate freelance writer interested in mysticism. Heard described the LSD effect as a 'shift in consciousness' that was 'so clearly similar to the accounts given by the mystics that none of us feels able to deny that this is in fact the experience which they undergo' (cited by Novak, 1997, p. 93). Cohen later started one of the earliest trials aiming to use LSD in psychotherapy (Cohen & Eisner, 1959).

In 1957, the Canada-based psychiatrist Humphrey Osmond keynoted a conference of the New York Academy of the Sciences titled 'The pharmacology of psychotomimetic and psychotherapeutic drugs' (Kety, 1957). His speech included the proposal to term hallucinogens such as LSD 'psychedelics',

meaning 'mind-manifesting'—a name that implies 'concepts of enriching the mind and enlarging the vision'. Osmond claimed that LSD and similar drugs did much more than simply mimic some symptoms of mental illness. Instead, they may give people insightful and pleasurable experiences that better enable them to understand themselves and their relationships with the world. Therefore, Osmond called for scientists to explore the social, religious, and philosophical applications of these drugs and to realize that 'psychedelics have a part to play in our survival as a species' and that they may 'help us to explore and fathom our own nature'. It was Osmond who gave mescaline to the famous English writer Aldous Huxley, whose response was enthusiastic (Huxley, 1954, 1980). Huxley also soon tried LSD, and deemed it a more profound experience than mescaline. He soon became part of the informal association of self-experimenters in the Los Angeles area (Stevens, 1987, p. 36). He envisioned LSD as a drug that could change the shape of humankind's self-knowledge, an agent to accelerate evolution to produce a more intelligent, loving, and spiritual race of people. There is still a sub-culture tradition using psychedelic drugs for spiritual purposes (cf. Badiner & Grey, 2002) and enhancing creativity (Stafford & Golightly, 1969; Dobkin de Rios & Janiger, 2003). In later years, Albert Hofmann (1983) himself suggested that the materialistic American lifestyle, with its resultant feelings of alienation from nature and lack of a meaningful philosophy of life, drew people to experiment with a drug that offered insight and the chance to transcend the mundane realities of everyday life.

None of the existing recreational drugs such as alcohol, opiates, and cannabis enjoys a philosophical underpinning in western society in the way that LSD does. LSD has been advocated as having a purpose other than simply to get high. For its users, the psychedelic experience is about enhancing and expanding perception, and offering a new way to see the world. '[My] heightened awareness saw through the static, one-dimensional, ego-constricted, false front which is the consciousness-contracted reality of the everyday world. This was no evasive flight *from*, but a deep probe *into* reality' (Solomon, 1964 p. X). LSD appeared to provide a numinous experience unmediated by a religious hierarchy or sacred texts. Those who were primarily attracted to LSD were creative individuals who sought out novelty, change, and insight into the human condition.

Due to the spread in the popular consumption of LSD in the early 1960s, the US Food and Drug Administration (FDA) initiated drug confiscations in 1962, when it raided several Los Angeles therapists and seized their LSD supplies (Novak, 1997). In 1963, Sandoz restricted LSD to researchers connected to the NIMH, which cut the number from over 200 to 70 (Scigliano, 1968) and only 3 a few years later. However, it was too late to stop the spread of LSD. In 1963 its popularity increased, due to the widely known events triggered by the research group of the Harvard professor of psychology, Timothy Leary, the

later 'LSD prophet' (Bryan, 1980; Forte, 1999; Greenfield, 2006). After undertaking scientific experiments and publications about the effects of psilocybin, he supported the view that psychedelic drugs could be used for 'consciousness-expansion' (Metzner, 1999). It was the famous beat poet, Allen Ginsberg, who introduced Leary to the concept of the 'fifth freedom': the right of all individuals to alter their consciousness. Because of misunderstandings, it has to be stated clearly that Timothy Leary never conducted any LSD research when employed at Harvard University (he used psilocybin).

The turmoil about psychedelic drugs broadened in the context of the rising student protests in 1966–1969 against the Vietnam War and against the prevailing materialistic American culture, the value system of which was increasingly brought into question (Lee & Shlain, 1985). This led to a kind of 'confrontation of generations' and the creation of the 'hippy' movement, which was definitely energized by the consumption of psychedelic drugs (Hunter, 1971; Stevens, 1987). Timothy Leary was sentenced to absurd prison sentences, and consumption of hallucinogens was put under threat of heavy penalties (Lee & Shlain, 1985).

Its prohibition created a need for new sources of LSD. Hence the rise of illegal laboratories and of the outlaw LSD chemist. It is not possible to give details about the activities of some idealists, who, believing in the power of the LSD experience to change the world for the better, illegally synthesized and distributed LSD since the late 1960s (cf. Tendler & May, 1984; Black, 1998; Roberts, 2008; Laing, 2003).

With regard to scientific investigations, the psychedelic movement has stimulated the serious study of altered states of consciousness, meditation, and religious experiences (Tart, 1969; White, 1973; Sugarman & Tarter, 1978).

Research restrictions and recent applications

The primary American sponsor of psychedelic drug research, the NIMH, curtailed its last intramural LSD project in 1968, after administering the drug to some 3,000 persons over a 14-year period. NIMH terminated its thirtieth and last extramural grant for LSD work with humans in 1974, having spent $4 million over 20 years. The NIMH claimed that it was disappointed by the results of this research, and that there were no longer any researchers interested in the field (Asher, 1975).

A scientist wishing to research LSD or related hallucinogenic substances in the United States must have his project approved through a complex, time-consuming process involving an Institutional Review Board (in Europe Ethics Committee) and two agencies, the FDA and the Drug Enforcement Administration (DEA) (cf. Strassman, 1992; Doblin, 2000). From the early 1970s to the 1990s, these

agencies refused permission to all researchers who applied. The system was not as strict in Europe, but the bulk of paperwork discourages many researchers from even bothering to apply.

Astonishingly enough, the NIMH Research Task Force recommended in 1974 that 'scientific study of hallucinogen-derived "mystical" experience should be encouraged', noting that researchers had largely ignored such experiences, despite their reputedly 'powerful' and 'transforming' qualities (Asher, 1975, p. 5). Thirty years later, a recent study followed this line of research, using psilocybin, with a methodologically sound design and impressive results (Griffith, *et al*., 2006). However, LSD remained beyond the pale of scientific research.

Recently, there has been a renewed interest in research with hallucinogenic substances, using psilocybin and methylenedioxymethamphetamine (MDMA, or 'Ecstasy') for psychotherapeutic purposes. There has also been progress in research with LSD. In 2007, the first permissions in recent times were given to a neuroscientific pilot study, using LSD with human participants, initiated by the Beckley Foundation in collaboration with UC Berkeley. Later in 2007, a study in Switzerland received approvals for using LSD-assisted psychotherapy in subjects suffering severe anxiety associated with end-of-life issues.

In recent years researchers found that LSD as well as psilocybin can help people with cluster headaches, a very severe condition, to attenuate their symptoms and extend their remission period from 6 to more than 18 months after only 1–3 doses (Sewell *et al*., 2006; Sewell and Halpern, 2007). More recently it was found that the non-hallucinogenic LSD-like compound 2-bromo-LSD can do the same without any hallucinogenic side effects (Karst *et al*., 2010). The mechanism of this astonishing extension of the remission period is still unexplained. It appears possible that LSD and 2-bromo-LSD are the first known agents which work directly on the regulation of gene expression (epigenetic level).

Thus there is reason for renewed hope that the intentions of its discoverer may become realized: 'I believe that if people would learn to use LSD's vision-inducing capability more wisely, under suitable conditions, in medical practice and in conjunction with meditation, then in future this problem child would become a wonder child' (Hofmann, 1983).

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Chapter 2

Pharmacological effects

Summarized overview

Basic substance:	LSD is a half-synthetic product of lysergic acid derived from the parasitic rye fungus *Claviceps purpurea*
Usage:	P.o. (dominant), i.m., i.v.
Effect:	Numerous vegetative, psychosensoric, and central effects.
Onset of effects:	At 1 μg/kg p.o. 30–45 min, at 16 μg/kg i.v. in a few minutes
Peak of effects:	1–3 h after oral administration.
Duration of effects:	Dose-dependent: at 1 μg/kg 6–8 h, at 16 μg/kg up to 10–12 h.
Action:	Interaction with post-synaptical 5-HT, dopamine, adrenaline, and other receptors.
Distribution:	Quick distribution from plasma into tissues (liver > kidney > spleen > brain > muscle > fat tissue).
Protein binding:	65–90% on plasma proteins.
Metabolites:	Nor-LSD, LAE, 2-oxo-LSD, O-H-LSD, 13, and, respectively, 14-hydroxy-LSD glucoronide, lysergicacidethyl-2-hydroxyethylamide (LEO), and trioxylized LSD.
Elimination:	Metabolization via liver. Presumably enterohepatistic circulation. Biliary excretion.
Half-life:	103 min.

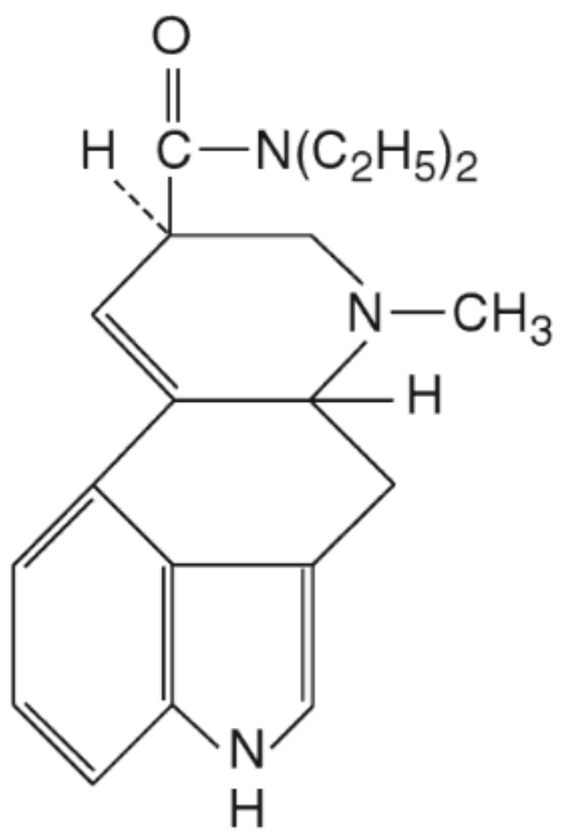

Fig. 2.1 Molecular structure of LSD.

Chemistry

Lysergic acid diethylamide is the diethylamide of lysergic acid. It is a half-synthetic substance, which can be obtained from the attachment of two ethyl groups to the naturally occurring lysergic acid. An indol ring and a tetracyclical ring system are built into the molecular structure (Ergolin). The psychoactive diethylamide derivative is related structurally to ergonovine, an isopropanolamide. Using a molecular formula of $C_{20}H_{25}N_3O$, a structural representation of LSD is shown in Figure 2.1.

In addition to lysergic acid, isomeric isolysergic acid is also found. The presence of two chiral carbon atoms present in the structure of lysergic acid results in the formation of four stereoisomers.

Pure LSD is a crystalline substance. It consists of colourless, prismatic crystals, with a melting point of 83°C. The molecule has an optical rotation of D^{20} = 30°C. LSD dissolves in water and pyridine, but not well, if at all, in organic solvents (Table 2.1). It is odourless and tasteless. The tartaric LSD is sensitive to light, which means it decays under the influence of daylight.

Table 2.1 Chemical data of LSD

Formula	$C_{20}H_{25}N_3O$
CAS number	50-37-3
PubChem	5761
Molar mass	323,42 g/mol
State of aggregation	solid
Melting point	80–85 °C (Base)
Solubility (H_2O)	soluble

From a pharmacological point of view as well as in relation to the effectiveness in humans, only dextro-LSD plays a role, because the levo-form as well as the levo- and dextro-derivatives of isolysergic acid are pharmacologically inactive (Cerletti & Konzett, 1956).

Radioisotopic labeling of LSD has been achieved for the purpose of metabolic studies and the mapping of LSD accumulation in a variety of tissues. The ^{14}C-isotope, for example, was successfully introduced into the dietylamide side chain (Stoll *et al*., 1954; Barnes 1974). [^{3}H]-LSD, incorporating the radioactive isotope tritium, is extensively used in many receptor binding studies by determination of its displacement from an investigated binding site. On the other hand, the use of a non-radioactive hydrogen isotope (^{2}H, deuterium) is particularly useful for analytical determinations of LSD and its derivatives in biofluids in which $^{2}H_3$- and $^{2}H_{10}$- LSD are commonly employed as internal standards (Reuschel *et al*., 1999).

Structure–activity relationships of some LSD derivatives

LSD is regarded as one of the most pharmacologically potent substances. It is effective in 1 μg/kg body weight. In order to discover the connection between chemical structure and psychological efficacy of the lysergic acid amides, the LSD molecule has been modified and substituted in different ways. These derivatives underwent pharmacological analysis in animal experiments and were tested on humans (Nichols, 2001, 1994). In order to compare the pharmacological characteristics and psychological effectiveness, Cerletti (1958b) chose 18 modified LSD products and presented their profiles schematically (Table 2.2).

The psychomimetic effectiveness is on the left-hand side in relative values, related to LSD = 100, applied logarithmically. These values mainly result from the tests by Isbell *et al*. (1959a); in part, they were ascertained by Hofmann (1958) in experiments on himself. In Figure 2.2, one can see that with the substitution of the diethylamide group by other amide groupings, the psychic effectiveness is still present, however always in a weakened form.

2-Bromo-lysergic acid diethylamide (BOL-148)

The most investigated lysergic acid derivative after LSD is bromo-LSD (BOL-148) (Table 2.3).

Whilst the strength of serotonin antagonism with LSD is comparable, it possesses almost no psychic effects (even in doses up to 20 μg/kg). The only psychic effect described was a feeling of tiredness and some psychophysical irritation at high doses (Cerletti & Konzett, 1956).

1-Methyl-lysergic acid butanolamide (UML-491, Methysergide)

1-Methyl-lysergic acid butanolamide is the strongest anti-serotonergic lysergic acid derivative, and it was used from the outset in the treatment of migraines

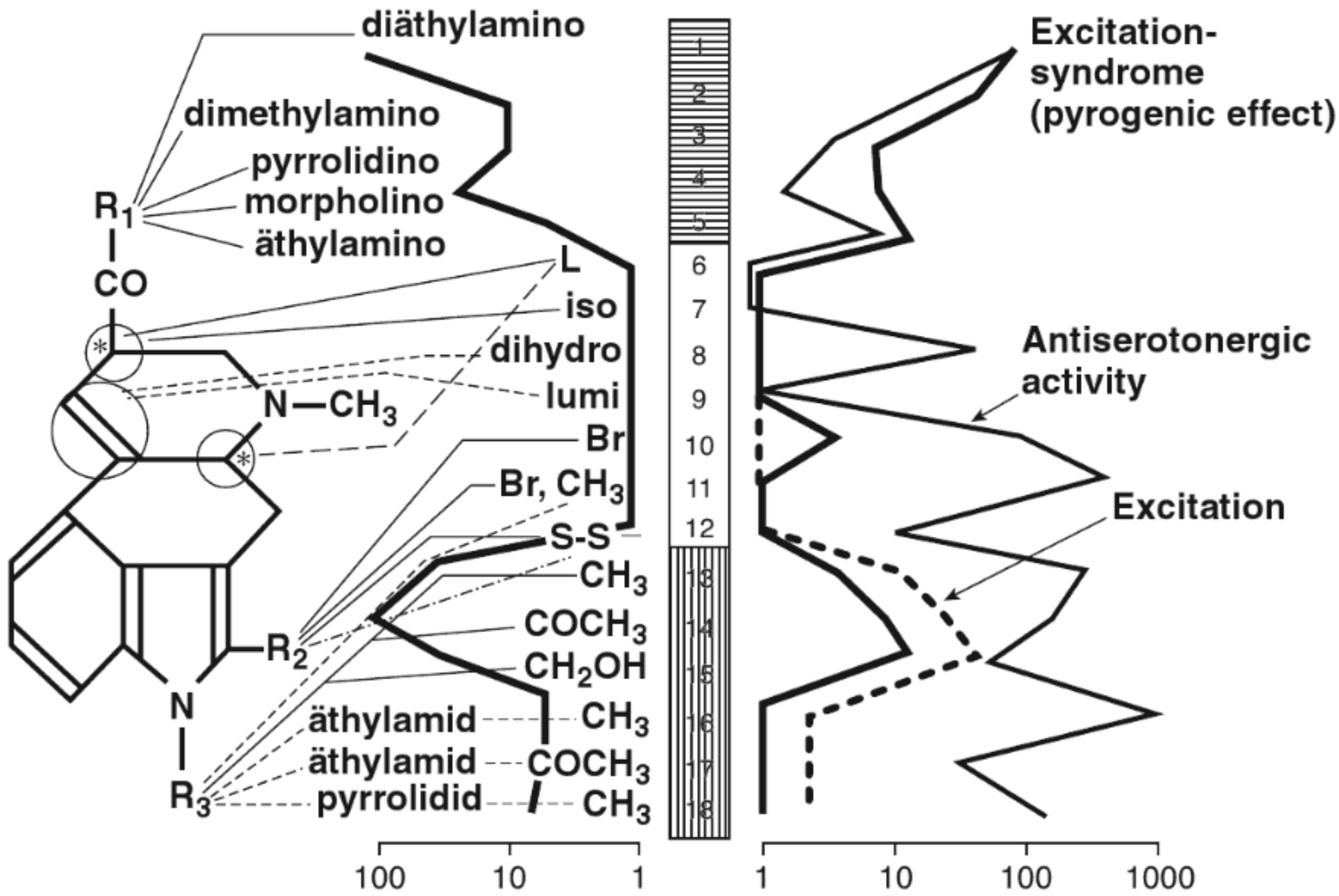

Fig. 2.2 Comparison of LSD and related substances (Hofmann, 2000, S. 190).

Table 2.2 18 derivates of LSD. The molecules 1–5 are variations at the acid amide group. The molecules 6–12 are stereoisomeres and molecules with different substituents at the ring structure of LSD, which leads to psychologically inactive substances. Molecules 13–18 show a number of different substituents present on the indole nitrogen. There are much more derivates of LSD (cf. Pfaff *et al.*, 1994) which are in some cases even more potent than LSD (Chambers *et al.*, 2001).

Lysergic acid derivative	**Code name**
d-lysergic acid diethylamide	d-LSD-25
l-lysergic acid diethylamide	l-LSD-25
d-iso-lysergic acid diethylamide	d-iso-lysergic acid diethylamide-25
lysergic acid dimethylamide	DAM-57
d-lysergic acid pyrrolidide	
d-lysergic acid morpholide	LSM-775
d-lysergic acid monoethylamide	LAE-32
di-hydroxy-d-lysergic acid diethylamide	
lumi-d-lysergic acid diethylamide	lumi-LSD-25
2-bromo-d-lysergic acid diethylamide	BOL-148
1-methyl-2-brom-d-lysergic acid diethylamide	MBL-61
di-lysergic acid diethylamide-disulfide	
1-methyl-d-lysergic acid diethylamide	MLD-41
1-acetyl-d-lysergic acid diethylamide	ALD-52
1-hydroxymethyl-d-lysergic acid diethylamide	OML-632
1-methyl-d-lysergic acid monoethylamide	MLA-74
1-acetyl-d-lysergic acid monoethylamide	ALA-10
1-methyl-d-lysergic acid pyrrolidide	LPD-824

and allergic reactions (Abramson, 1965). The critical dose for the creation of psychic effects is 150 times higher than with LSD (Abramson, 1959).

The effects of UML-491 are similar to those of LSD, although the effect on psyche and autonomous nervous system is strongly blotted out due to vasomotoric effects (Abramson, 1965).

1-Methyl-lysergic acid diethylamide (MLD-41)

Methylation of the indole nitrogen of LSD reduces psychoactivity significantly (Malitz *et al.*, 1960). 1-Methyl-lysergic acid diethylamide counts as one of the most potent antiserotonergic substances from the lysergic acid derivative group (Cerletti & Doepfner, 1958). It creates psychic effects; however, the dose needed to reach a comparable strength of effect to LSD is three times as high (Abramson, 1959).

Lysergic acid morpholide (LSM-775)

Replacing the diethyl side chain of LSD with a morpholine group produces lysergic acid morpholide. This can induce similar, but less distinct effects than LSD (Gogerty & Dille, 1957).

Acetyl-lysergic acid diethylamide (ALD-52)

Acetylization of the indole nitrogen of LSD gives a derivative that show about a 50% drop in potency when compared to LSD. (Malitz *et al.*, 1960). With regard to serotonin, it functions almost equally strongly on isolated rat's uterus as LSD (Cerletti & Konzett, 1956).

Lysergic acid monoethylamide (LAE-32) and lysergic acid amide (LA-111)

LAE-32 is the monoethylamide derivative of LSD in which one ethyl group of the diethylamide is replaced by a hydrogen atom. With LA-111, both ethyl groups of LSD are replaced with hydrogen atoms. Experiments by Solms (1956) on 14 test persons with different doses of LAE-32 and LA-111 showed that 10 times the amount of LAE-32 was needed to trigger distinctive symptoms of equal magnitude. Clear differences in quality were observed. In the case of LAE-32 (0.5 mg, i.v.), the dominant symptoms were abulia, apathy, and mild dazed states; optical hallucinations appeared much less often in comparison. No principle differences could be found between LAE-32 and LA-111. With LA-111, lack of drive and an increasing clouding of the conciousness (without hallucinatory effects) were observed along with neuro-vegetative disruptions such as hypersalivation, vomiting, and diarrhoea. The separation of the two ethyl groups reduced the potency of LSD by a factor of 5 (starting from the given dose) and by a factor of 10 with reference to concentrations in the brain (Gessner & Page, 1962; Vogel *et al.*, 1972).

Table 2.3 Comparison of pharmacological effects of LSD and BOL-148 (Rothlin, 1957a)

Functions	**LSD**	**BOL-148**
Uterus and vagina in rabbit	Contraction (approx. 1.5 times weaker than ergometrine)	No contraction, inhibition of spontaneous rhythm and relaxation
Adrenolytic action (on seminal vesicle of guinea pig)	50 times weaker than ergotamine	10 times stronger than LSD
Blood vessels (perfused kidney of rat and rabbit)	Constriction	No effect
Blood pressure in anaesthetized cat	Decrease	No effect
Heart rate in anaesthetized cat	Bradycardia	No effect
Eye	Mydriasis	No effect
Body temperature (rabbit, cat, dog)	Increase in all doses	Decrease with high doses
Body temperature (rat)	decrease; increase with toxic doses	decrease with all doses
Blood sugar in rabbits	Increase	No effect
Behaviour in mice	Excitation	Sedation
Amphetamine excitation in mice	Potentiation	Inhibition
Effect on walzing mice	Inhibition on walzing	Inhibition (due to sedation)
Effect on EEG (humans)	Activation	No effect
Psychic action in humans	strong	absent
5-HT constriction on rat uterus and perfused blood vessels	Inhibition	Inhibition
5-HT constriction on bronchial musculature *in vivo*	Inhibition	Inhibition
5-HT-potentiating action to hypnotics in mice	Inhibition	Inhibition
Reserpin-potentiating action to hypnotics in mice	Inhibition	No inhibition
Effect on chromatophores of *Poecilia reticularis*	Spreading	Spreading (2.5 times as strong as LSD)
Effect on cholinesterase of brain slices *in vitro*	Inhibition	Inhibition

LSD modifications at the C-9/C-10 double bond

When the double bond between C-9 and C-10 is saturated, as is the case with dihydro-(+)-LSD, LSD-like autonomic and psychological changes are brought to the fore, which, however, act much more weakly and slowly (Gorodetzky & Isbell, 1964). Cerletti and Konzett (1956) observed a 1.6 times weaker effect with this substance than with LSD. Lumi-LSD ($C_{20}H_{27}O_2N_3$) can be formed by the addition of water at the C-9 and C-10 double bond. Its psychoactive effects are 100 times weaker than LSD (Cerletti & Konzett, 1956).

N-Amide-substituted derivatives of lysergic acid

The mono-substituted ethyl-, propyl-, and isopropylamides proved to be, respectively, 8.5, 2.5, and 5 times weaker in psychic effect than LSD. The butylamide of lysergic acid is the most effective compound in this group and only 1.5 times weaker in terms of antiserotonergic properties.

The di-substituted dimethyl-, diisopropyl-, and dibutylamides are 3–5 times weaker in effect on rat tissue as LSD. Lysergic acid pyrrolidide, which is formally represented as a closed-ring LSD molecule, is 20 times weaker than LSD (Cerletti & Konzett, 1956).

Other lysergic acid derivatives

D-L-1-Methyl-2-bromine-LSD (MBL-61) was 5 times more anti-serotonergic in animal experiments than LSD; however, in human experiments, even doses of 175 µg/kg showed no effect (Isbell, 1959).

Iodine-LSD is iodinated in position 2 and is only half as effective in relation to psychic effects, as well as to serotonin antagonism, as LSD itself (Cerletti & Konzett, 1956). 1-Oxymethyl-LSD represents a further derivative, which also possesses a weaker psychic and anti-serotonergic effect than LSD (Cerletti & Konzett, 1956).

Using mild halogening substances, LSD can be halogenated in position 2 of the pyrrol ring of the indol system, which leads to the elimination of the psychic activity (cf. Pfaff *et al*., 1994). The effect inhibiting serotonin remains untouched and even increases in comparison with that of LSD. Analogously to halogenation, an oxidization on the 2 atom leads to a pharmacologically inactive compound. In general, it can be understood from the presented data that a change in the chemical structure of LSD can lead to quantitative as well as qualitative changes; however, the potency is always less than that of LSD in comparison (Figure 2.3). The most significant of these LSD-like substances are those having substituents on the indol ring, namely 1-methyl-, 1-acetyl-, and 2-bromine-LSD, which possess a stronger antiseronergic activity than LSD (Rothlin, 1957b).

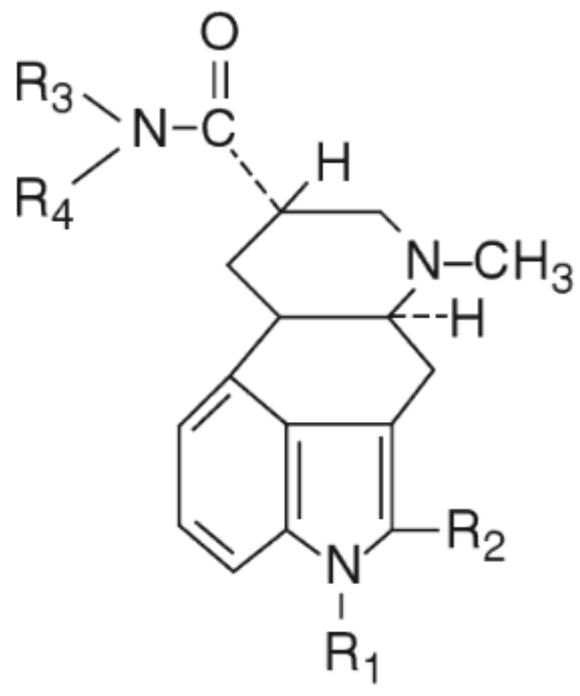

Fig. 2.3 Schematic representation of the chemical structure of lysergic acid.

Table 2.4 shows a number of substances, as well as their antiserotonergic activity, which were chemically modified out of lysergic acid and tested in humans. The first column gives relative strengths of the derivatives (Abramson, 1965). The second shows antiserotonergic activity (Cerletti, 1963).

The position 4 of the indole nucleus appears to play a special role in psychoactivity. Molecules in which carbon is combined with more atoms possess higher psychoactivity. Mescaline, for example, can be indolized *in vitro* and may possibly be indolized in the body; however, it cannot form these 4-substituting indol derivatives (Cerletti, 1963). Psilocybin has one phosphate group in position 4 of the indole ring. With LSD, this position is incorporated in two rings and thus forms the most stable connection/compound for the carbon atom. The comparable doses of these three psychoactive substances are 500 mg (Mescaline),

Table 2.4 Relationships of the chemical structures of LSD and some congeners to certain pharmacological actions

Compound	R_1	R_2	R_3	R_4	Psychotomimetic effect	Serotonin antagonism	Pyretogenic action
d-LSD-25	-H	-H	$-C_2H_5$	$-C_2H_5$	100	100	100
l-LSD-25	-H	-H	$-C_2H_5$	$-C_2H_5$	2***	0***	0***
ALD-52	$-COCH_3$	-H	$-C_2H_5$	$-C_2H_5$	91**	210**	13*
BOL-148	-H	-Br	$-C_2H_5$	$-C_2H_5$	0,72**	103*	5*
MLD-41	$-CH_3$	-H	$-C_2H_5$	$-C_2H_5$	40*	370*	5*
UML-491	$-CH_3$	-H	-H	C_2H_5 -CH CHOH	0,66**	400*	-
LAE-32	-H	-H	-H	$-C_2H_5$	3,4**	12**	18***

(*Rothlin, 1957a; **Abramson, 1965; ***Jarvik, 1967)

20 mg (Psilocybin), and 0.1 mg (LSD). Apparently, the human body does not possess an enzyme that can split this group and quickly detoxify these substances.

This hypothesis was supported by the observations of Heacock and Mahon (1964), who were able to identify all four isomers of hydroxyskatol. They found the 5-, 6-, and 7-isomers in the bodies of most people; however, there was no indication of the existence of the 4-hydroxy derivatives. The 5-hydroxyskatols were there in patients and in controls to the same degree, whilst the 6- and 7-hydroxy derivatives appeared more in psychiatric patients.

Pharmacokinetics

Resorption

The i.v. injection is pharmacologically the safest and best reproducible way to administer LSD. Thus, biological availability is 100%. In fact, this only plays a role in experimental research. If 40–180 μg of LSD is administered via i.v., astonishingly, it takes a few minutes until the effects begin, reaching a maximum after 1 h (as in peroral administration). Via slow i.v. application, it can take up to 20 min for the first effects to occur. The length of effect is given at 9–10 h (Boyd *et al*., 1955a; Lanz *et al*., 1955; Hoch, 1956b). The tartrate of LSD can be dissolved in water and is quickly and fully absorbed (Rothlin & Cerletti, 1956; Rothlin, 1957b). After an oral application of 100–250 μg LSD, the effect appears after 30–45 min, reaching its maximum after 1.5–2.5 h and lasts 9–12 h (Hoch, 1956b).

In a study, 13 test subjects received different amounts of food before taking LSD (160 μg, p.o.). At each control time, LSD level was half as high in those having had a sumptuous meal, than in those with empty stomachs. Those who had had a light meal showed values that lay between both extremes. This implies that the size of the meal, the pH values of stomach and duodenum, as well as the gastric evacuation rate, have an influence on the absorption of LSD (Upshall & Wailling, 1972).

Using the same dose, lower serum concentration was reached after i.p. application in rats than after i.v. application; the distribution pattern remained the same (Boyd, 1959). Only 10–20% of the given dose reached the systemic circulation (Boyd *et al*., 1955b). After both intrathecal (Freedman, 1984) and intraspinal injections (Hoch, 1956b) the first autonomous effects were observed in 1–2 min. With intramuscular injection, first symptoms appear after 15–20 min, reach their maximum after 1 h and last for 9–10 h.

Distribution

Apparently no human studies were carried out on this. Therefore only results of animal experiments are given here. Practically all radioactivity in form of

^{14}C-marked LSD (50 µg, i.v.) disappeared from the blood of mice within a few minutes, reaching a maximum in most organs after 10–15 min. Within a few hours, no radioactivity could be detected in body compartments. In the duodenum, the activity increased strongly in the first two hours (about 50% of the dose). The radioactive-marked LSD moved along with the contents of the intestine, and after 2–3 h greatest activity is in the colon (Stoll *et al.*, 1955). The gastrointestinal section contained about 70–80% of the radioactive-marked LSD, or rather its metabolites, after about 3–12 h (Boyd *et al.*, 1955a; Boyd, 1959).

With mice, the LSD content in the liver was greater than in the blood after 10 min following LSD administration (35 mg/kg, i.v.). However, the ratio of tissue-LSD to blood-LSD was constant (Lanz *et al.*, 1955). Because the substance level in the liver only sinks slowly within 12 h, an enterohepatic circulation was supposed (Boyd *et al.*, 1955a; Boyd, 1959).

None of the tissues, with the exemption of blood, changed its relative concentration of radioactive substances more than twice, even at 100 times the dose. The relative blood–plasma level fell by a factor of 7 with diminishing doses. The gall acids did not significantly change their concentration of radioactivity (Boyd, 1959).

No significant difference could be found between concentrations in rat skeletal muscle and serum concentrations (Lanz *et al.*, 1955). An appreciably lower LSD concentration was found in the brain than in the serum, this also sank more quickly, independently from the blood speculum (Lanz *et al.*, 1955). An astonishing fact, which still defies explanation, is that the brain concentration of LSD in rats (at maximum effect) was 1.000 times lower than it was in the blood plasma (Rosecrans *et al.*, 1967; Freedman & Boggan, 1974).

Arnold *et al.* (1958) tested the distribution of LSD in the organism using ^{14}C-marked LSD (8–12 mg/kg i.p.) in mice. The liver, gall capillaries as well as the bile ducts show the highest ^{14}C-LSD activity, corresponding to the excretion of LSD via bile into the intestine. In addition, intracellular activity in numerous liver cells was visible, in which, however, not all sections were evenly affected.

The kidney's glomeruli and tubuli showed a particularly high level of activity.

In autoradiographics, parallel to a diffuse activity in all parts of the brain, a varied distribution of ^{14}C-LSD showed up. It appeared, listed in decreasing order, in the structures of the hippocampus, basal ganglia, the central substantia grisea, the cerebral cortex, and the cerebellum (Figure 2.4). In most cases, activity within the ganglia cells was spread out like a net over the outer shell of the cell, whereby the core area remained free, whilst in numerous other brain cells the core also showed central activity (Arnold *et al.*, 1958). The distribution of LSD (1.3–10 mg/kg i.v.) and UML-491 (3–30 mg/kg i.v.) in rats was specified to

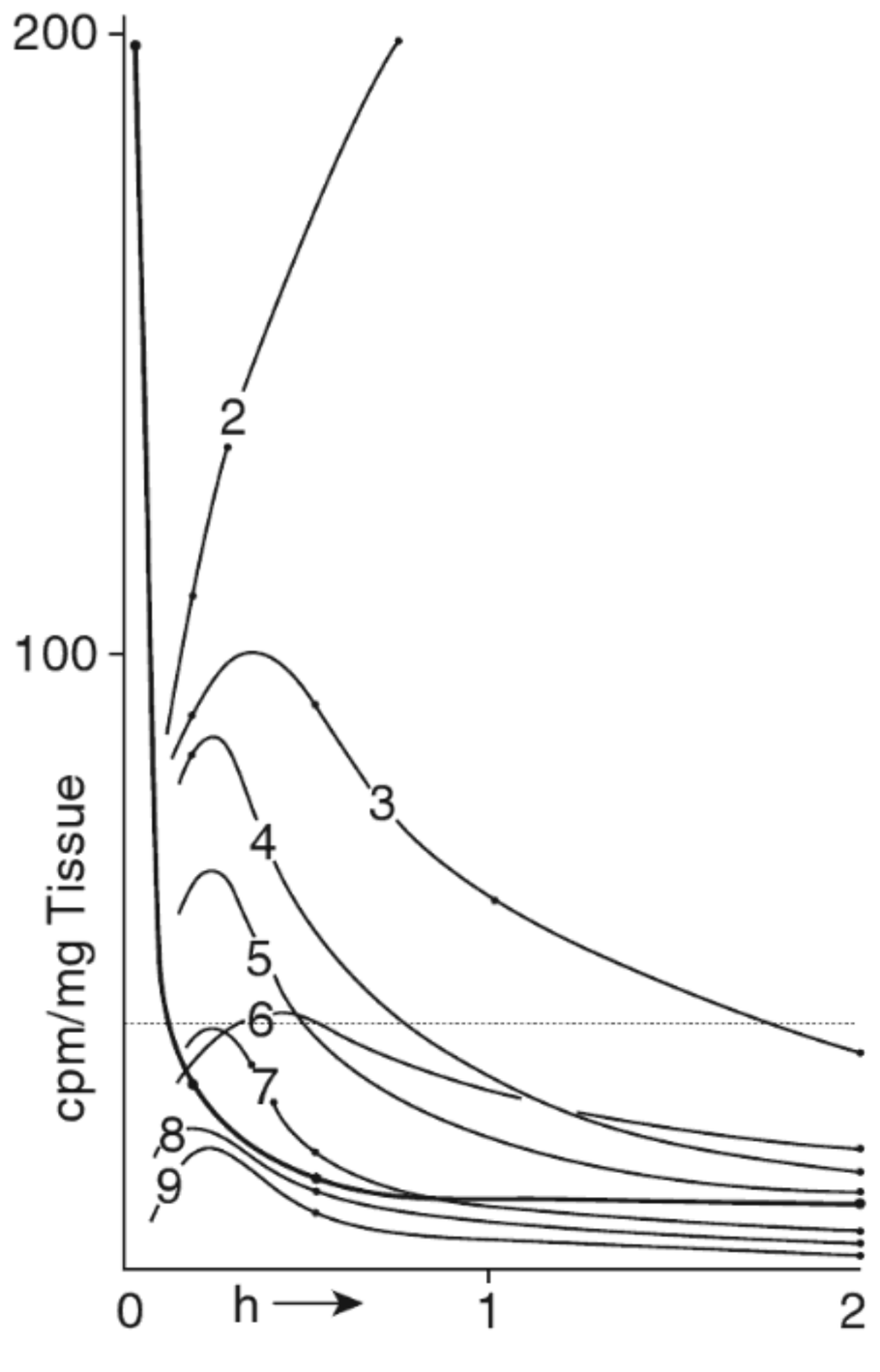

Fig. 2.4 Distribution and excretion of C^{14}-LSD in mice. 1 blood; 2 duodenum; 3 liver; 4 kidney, adrenal gland; 5 lung, spleen, pancreas; 6 gut; 7 heart; 8 muscle, skin; and 9 brain (Hofmann, 1964, S.188).

a serotonin antagonist, using fluorometric analysis. Based on the determined tissue/blood quotients, it could be ascertained that both lysergic acid derivatives shared the same distribution pattern in lungs and muscles. In contrast to this, in the UML-491 in the brain only about 13% of the value of LSD could be detected. Leading from this, it was discussed whether LSD could pass the blood–brain barrier more easily than UML-491 (Doepfner, 1962).

Haley & Rutschmann 1957 investigated radioactivity in the brain, liver, and small intestine of mice after i.v. and intracerebral injection of ^{14}C-LSD (25 μg). The result was such that the radioactive injection appeared in the liver and was excreted via the bile in the small intestine, just as fast as the i.v. application. Because a minimal LSD activity in the brain could be measured after the i.v. injection, it was deduced that the blood–liquor barrier hampered the advance of LSD into the brain tissue to a great extent, but did not disturb the exit of the compound from the brain. The rapid fall in concentration in the brain after intraventricular injection was confirmed in experiments on cats (50 μg/kg) (Haley & Rutschmann 1957).

Hoagland (1956) reported similar concentrations of radioactively marked LSD (100 μg, i.p.) in rat brains, as did Arnold *et al*. (1958). In the cortex and hypothalamus the levels were somewhat lower, whereas higher in the cortex.

The liver showed levels about 4 times higher than in the whole brain as a whole. Axelrod *et al*. (1957) could not find any difference in the level of concentration within single parts of the brain. By contrast, other authors reported particularly high amounts in the hypophysis and epiphysis, as well as in the subcortical structures in rats (Freedman & Coquet, 1965) and apes (Snyder & Reivich, 1966), which indicates a connection with the autonomous and limbic system. Compared with the reflex centres and the chiasma opticum, considerably less LSD was found in the structures of the visual cortex (Freedman, 1965; Snyder & Reivich, 1966). After several hours, Diab *et al*. (1971) were able to identify remaining LSD bonds on several areas of the brain, as well as in the plexus choroideus, using autoradiographic methods.

In two studies, the distribution of LSD (1 mg/kg, i.v.) in cat tissue was investigated spectrofluorometrically. The highest concentrations were found in the gall bladder and the blood plasma, followed by the lungs, liver, brain, gastrointestinal tract, spleen, liquor, and muscles. Lowest concentration was found in fat tissue (Axelrod *et al*., 1957; Boyd, 1959).

Volume of distribution

One possibility for finding out about the distribution of a substance in body compartments is to investigate its distribution volumes. This is to be understood as the size of a space in which the substance is distributed, meaning the accumulation dynamics of a substance in certain tissues.

Wagner *et al*. (1968) developed an open two-compartment model for the relationships between plasma concentration and the pharmacological effects of LSD. Some authors also busied themselves with this model, but other data were congruent with those of Wagner's. Using mathematical methods, it was tried to construct a complete pharmacokinetie model. Out of the data obtained, the relationship between the effect and the concentration of LSD in tissue could be either linear, or rather logarithmically linear, or it could point to neither of these possibilities (Metzler, 1969). This opinion faced growing criticism that it was based on a false calculation, which led one to believe that a direct proportional relationship existed. It was further argued that LSD's place of effect should be treated as a totally self-sufficient compartment (Levy, 1969).

Blood–brain barrier

Wright (1972), carrying out *in vitro* experiments on the plexus choroideus of bullfrogs, showed the temporal progress of [^{3}H]-LSD accumulation. After a strong initial rise, the accumulation reached its steady state after 3 h. There was no indication of LSD (3 μM) adhering to the tissue. This accumulation was reduced using ouabain (strophanthine), iodoacetate/cyanide, and a temperature

of 0°C at 65%. The influence of ouabain pointed to a connection with Na^+/K^+-ATPasis. Decamethoniumbromine (1 μM), a quartile amine, reduced the LSD uptake by 50%. Since quartile amines competitively inhibit the accumulation of primary and tertiary amines, Wright (1972) assumed an amine carrier to be responsible for the active accumulation.

[^{3}H]-LSD dispersed evenly over the ventricular and serous surface of the plexus, in contrast to amino acids, which accumulated only on the ventricular side. Since the allocation of LSD was even on both sides, it was presumed that the plexus choroideus was not a preferred site for accretion.

More than 75% of the accumulated isotopes could be eluted in solution, so that this fraction was presumably not irreversibly linked to cellular structures. In another experiment, 80% of the [^{3}H]-LSD moved during thin-layer chromatography, which implied that this fraction accumulated freely at the plexus and the rest was linked to tissue proteins. Analyses with iodoacetate/cyanide showed a slight rise in the unidirectional flow. The absence of a significant discrepancy in the unidirectional LSD flow along the plexus choroideus makes it unlikely that it is actively transported along the choriodal epithelium.

Hoff and Arnold (1959) carried out investigations with ^{14}C-LSD in mice. They demonstrated that LSD passes the blood–brain barrier and is detectable in the brain (albeit in a concentration lower than in the liver, spleen, kidney, and adrenal gland).

Autoradiographic studies concerning the allocation of LSD in rat brains showed that the plexus choroideus participated in the passage between the blood–brain barrier. It is possible this structure is involved in the active transport of LSD between blood and liquor (Diab *et al.*, 1971). Axelrod *et al.* (1957) administered LSD to monkeys (0.2 mg/kg, i.v.) and took samples of blood and liquor at different time intervals. The LSD concentration in the liquor peaked 10 min after administration and declined continuously during the following hours (Figure 2.5). The ratio of LSD in the liquor compared with the much higher concentration in the blood plasma is consistent with the fraction which is not bound to plasma proteins (10–35%). Thus, the binding to plasma proteins could be the primary obstacle for LSD when passing the blood–brain barrier.

Protein binding

Up until now, there have been no human studies on the protein binding of LSD. Lanz *et al.* (1955) ascertained a decrease in LSD concentration to 21% after 17 h in *in vitro* investigations with mouse brains. It could not be explained whether this difference came out of the increasingly strong binding of the LSD

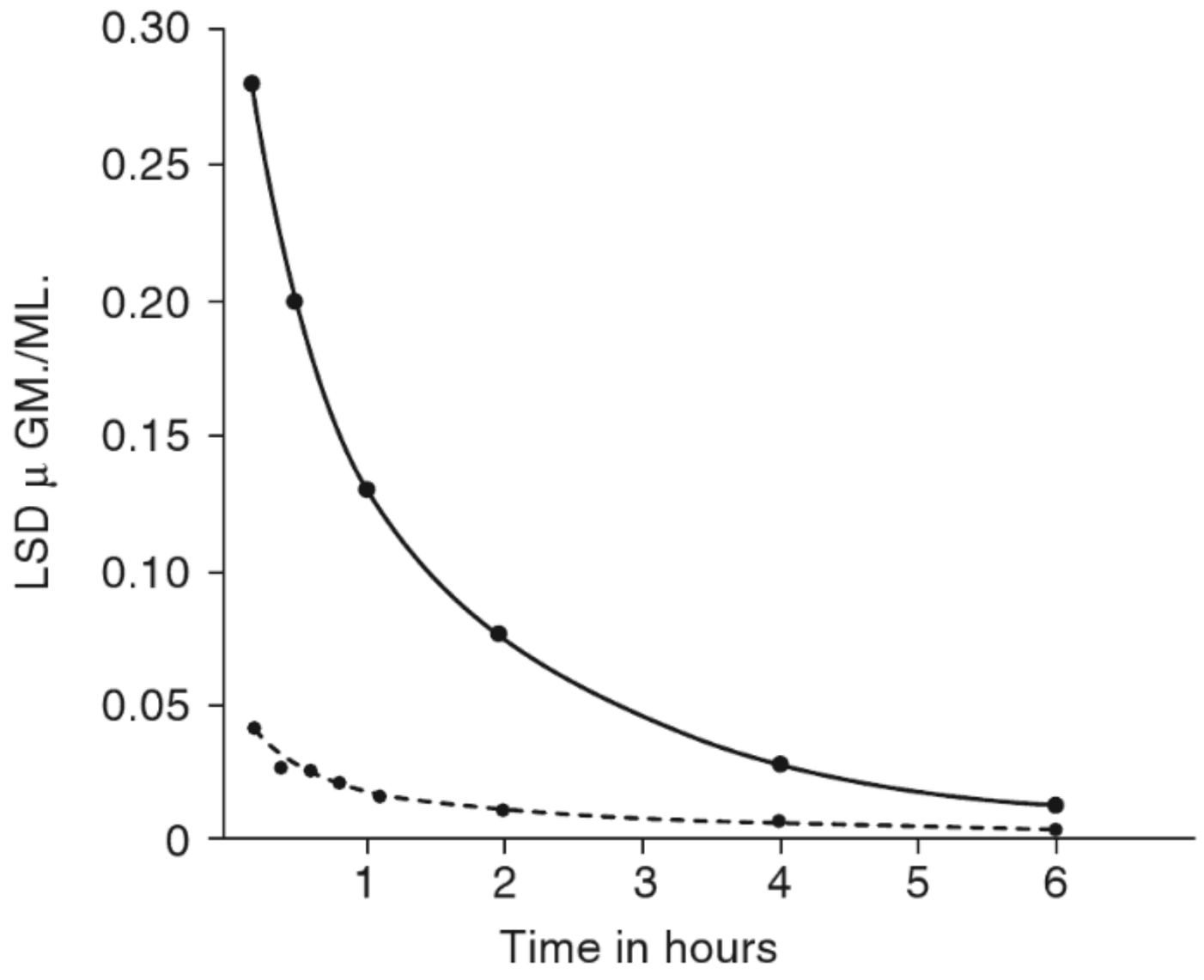

Fig. 2.5 Plasma (——) and cerebrospinal fluid (- - - -) levels of LSD after the i.v. administration of 0.2 mg/kg LSD in a monkey (*Macaca mulatta*) (Axelrod *et al.*, 1957 with permission from Wiley-Blackwell publishers).

to the protein or alone through metabolization. After division of the constituent parts, there was 10–30% of the blood radioactivity in the cellular fraction, if the rats were treated with ^{14}C-marked LSD (1 mg/kg, i.p.). The plasma protein-connected part of the radioactive fraction deceases with time; after 5 min, 70% are still bonded, after 3 h only 40% (Boyd, 1959). Keup (1959) examined the bonding of protein [^{14}C]-LSD (3.1 mg/kg, i.p.) in rats. After its distribution in the body, the radioactively marked LSD was washed out and only the protein-bonded portion remained. In the first hours after injection, protein binding was highest in lung tissue; however, the quickest increase was found in liver proteins, with a peak after 2 h. In the brain, it was highest after 6 h. Through *in vitro* examinations on cat tissue, Axelrod *et al.* (1957) were able to prove the attachment of LSD (plasma concentrations 0.1–20 mg/l) to plasma proteins. After dialysis of the plasma (against an isotonic phosphate barrier of pH value 7.4), 65–90% of the LSD was bonded to non-diffusible parts of the plasma.

Plasma levels

Virtually all the applied radioactivity (50 µg ^{14}C-LSD, i.v.) disappears within a few minutes from the blood of mice (Stoll *et al.*, 1955). After a strong initial decay, the blood level in mice sinks linearly 20 min after intravenous application (Lanz *et al.*, 1955).

Fang *et al.* (2003) analysed the LSD concentration in the serum of mice by means of electrophoresis fluorescence spectroscopy. After 20 respectively

Table 2.5 Clinical pharmacokinetics of LSD with different modes of application (data from Hoch, 1956b) (number of subjects not reported)

Mode of application	Dose	Onset of symptoms	Peak effect	Total duration
Per os	100–250 µg	30–45 min	1.0–2.5 h*	9–12 h
Intramuscular	100–250 µg	15–20 min	1.0 h*	9–10 h
Intravenous	40–180 µg	3–5 min	1.0 h*	9–10 h
Intraspinal	20–60 µg	< 1 min	1.0 h*	9–10 h

* Hours after application of LSD.

60 min after ingestion of 0.1 mg LSD p.o. 120 respectively 30 ng/ml LSD were detected in the serum.

The relation between plasma and liquor concentration of LSD was demonstrated in a monkey experiment (0.2 mg/kg, i.v.). According to this, the LSD plasma level declined particularly quickly within the first hour after application (as an indicator of the substance's passage into the tissue compartments). In the liquor, LSD peaked after 10 min, and declined slowly (Axelrod *et al.*, 1957). Different modes of application lead to different times of onset of effect with intraspinal application being the fastest (Table 2.5).

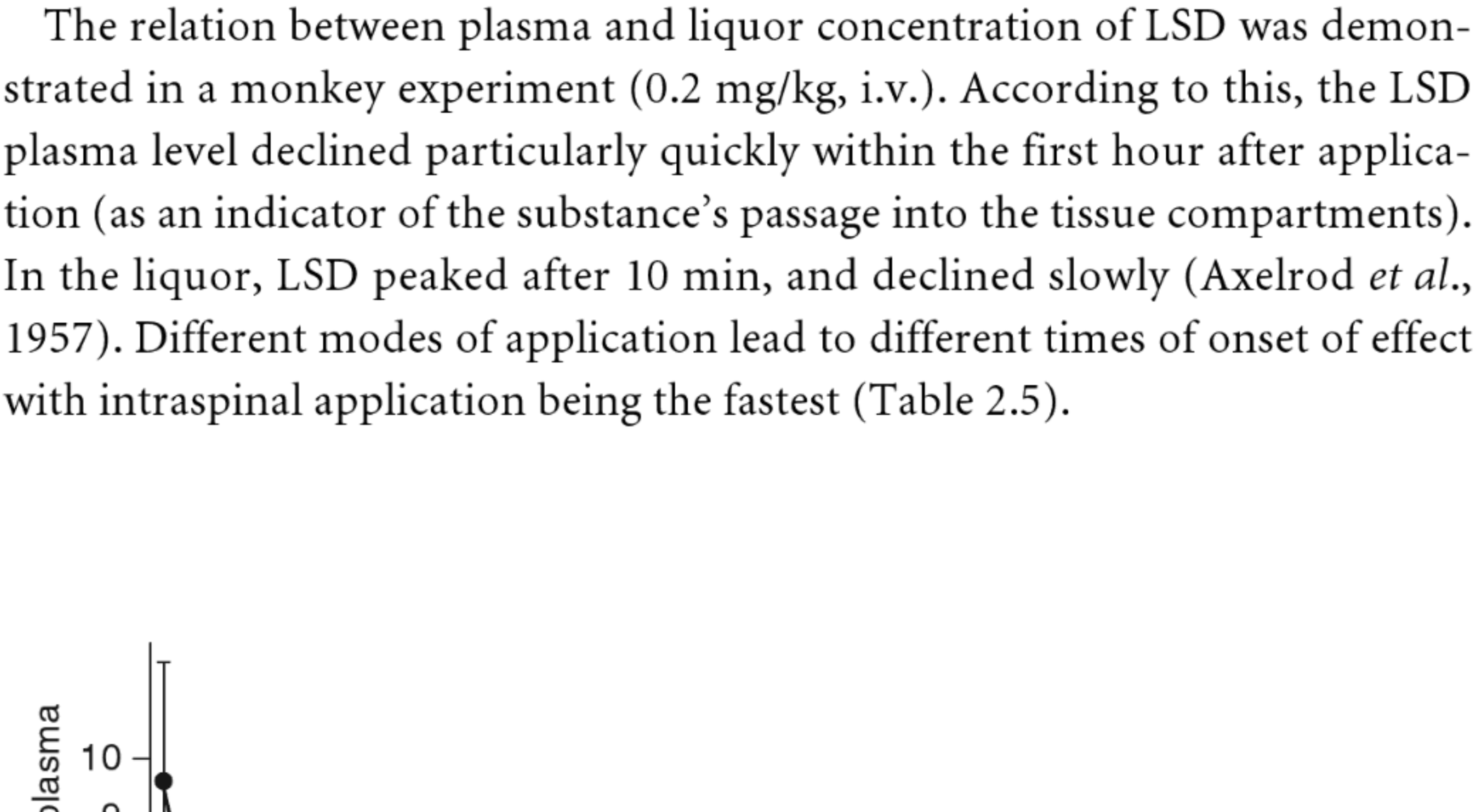

Fig. 2.6 Course of plasma levels of LSD after 2 µg/kg i.v. in humans (Aghajanian and Bing, 1962).

Blood samples were taken from five test subjects at different times after LSD administration (2 μg/kg, i.v.), in order to analyse them by means of spectrophotofluorometry. A large decrease of LSD plasma levels Digestin in urine (plasma levels human) was observed within the first 30 min, followed by a slow descent in concentration. Within 30 min, an equilibration was reached (plasma level 6–7 ng/ml). The rapid decay was interpreted as a substance reallocation from plasma into tissue. During the following hours, the LSD plasma level fell evenly, with test score performance improving (Aghajanian & Bing, 1964).

Metabolism

Some metabolites of LSD have definitely been ascertained (see Figure 2.7); however, a consistent path of metabolization could not yet be eruded. Only about 1% of the LSD is excreted unchanged in human urine (Siva Sankar, 1975; Canezin *et al*., 2001; Wölfel, 2001). LSD is oxidized to 2-oxy-LSD by the liver's NADH-dependent, microsomalic enzyme system. Only liver tissue metabolizes LSD (Axelrod *et al*., 1957). Hoffer (1965) described that LSD activity dropped by 50% in the liver, as well as in muscle homogenates of rats within a few minutes. During the next 17 h, only very little LSD was metabolized.

Brain homogenates reduced the activity of LSD to 58% after 10 min and to 80% after 17 h. The same results were observed at 3°C, as well as at 38°C. Boyd (1959) found that, at 1 mg/kg LSD, the liver shows its maximum metabolism rate in the beginning. Also at higher doses (1.5–2 mg/kg) the metabolism rate in the beginning was not higher. Therefore, the metabolism rate of a rat's liver was calculated to be 0.9 mg/h LSD. Niwaguchi *et al*. (1974a) showed that the conversion of LSD in rat-liver preparations stops after 100–120 min.

The optimal pH value for the maximum activity for metabolizing enzymes lay between 7.2 and 7.6. For the optimal metabolism of LSD microsomes, 'supernatant fraction', NADP and nicotine acid were needed. Under anaerobic conditions, metabolism only went extremely slowly. From their data, Inoue *et al*. (1980) concluded that LSD metabolism was catalysed by three different enzyme systems. After the incubation of LSD with liver microsomes from untreated rats, SKF 525-A (β-diethylaminoethyl–diphenylpropylacetathydrochloride, inhibitor of the hepatic monooxygenase) significantly inhibited the hydroxylation of LSD at position 13. There was also a moderate inhibition of the N-demethylization at position 6, as well as the N-deethylization at position 8 of the molecule. In an atmosphere containing 80% CO and 20% oxygen, the N-demethylization was inhibition at its maximum, the 13-hydroxylation moderate and the N-deethylization of the side chain only weak.

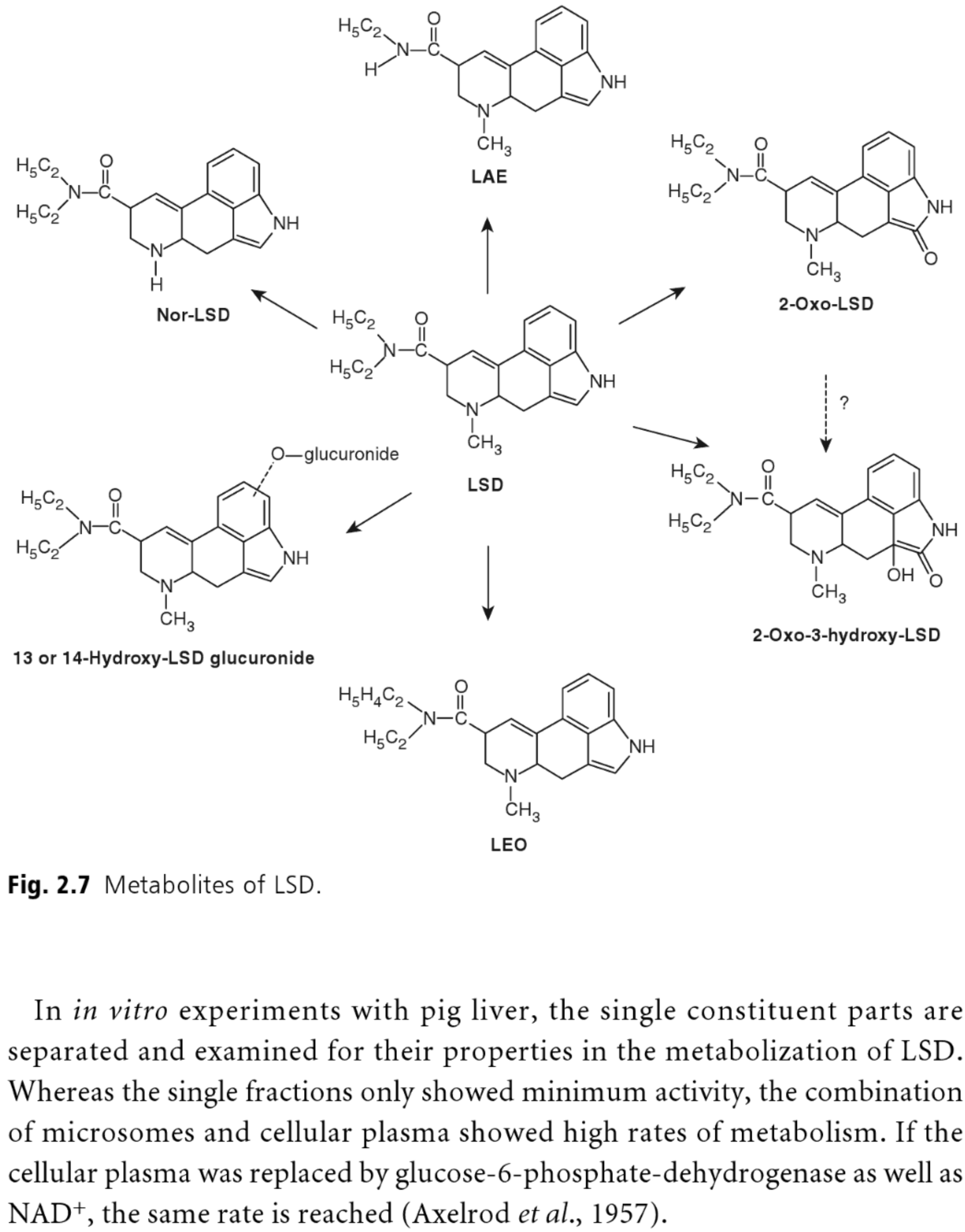

Fig. 2.7 Metabolites of LSD.

In *in vitro* experiments with pig liver, the single constituent parts are separated and examined for their properties in the metabolization of LSD. Whereas the single fractions only showed minimum activity, the combination of microsomes and cellular plasma showed high rates of metabolism. If the cellular plasma was replaced by glucose-6-phosphate-dehydrogenase as well as NAD^+, the same rate is reached (Axelrod *et al.*, 1957).

Metabolites

In the human body, LSD is rapidly degraded to its structurally related metabolites (Niwaguchi *et al.*, 1974b; see Figure 2.7). Extraction experiments with added inactive LSD showed that a greater part of LSD is metabolized within the organism. Three different, as opposed to LSD water-soluble radioactive degradation products, could be characterized by their Rf value (0, 0.13, 0.18) (Stoll *et al.*, 1955).

Boyd *et al.* (1955a), by means of a chromatographic analysis of bile acid, showed two potential metabolites, M1 (Rf: 0.23) and M2 (Rf: 0.15), besides

LSD (Rf: 0.83), and furthermore two radioactive spots with Rf values of 0.6 to 0.9. The two components, M1 and M2, accounted for 60% of the bile acid's total radioactivity and could be detected in urine as well. In the infrared spectrum, M1 and M2 were distinguishable from LSD, Lysergic acid amide (LAE), and lysergic acid. Tests with fluorescence and Ehrlich's reagent showed that the metabolites still had a ring structure. The continuing radioactivity indicated the presence of a diethyl component. It remained unclear whether M3 was a metabolite or unmodified LSD. M4 was not found in all samples and it was presumed that it was a spare product of M1 and M2 (Boyd, 1959).

Slaytor *et al*. (1959), using paper chromatography, were able to prove two metabolites with different polarity in rats' gall bladders (LSD 3 mg/kg intravenously, Rf: 0.77). The more polar metabolite (Rf: 0.1) was produced in much higher amounts than the other (Rf: 0.14). Both LSD metabolites antagonized 5-HT in an isolated rat uterus preparation. It seemed that these were hydroxylated and conjugated derivatives of LSD.

Niwaguchi *et al*. (1974b) identified M1 as lysergic acid monoethylamide, which originated from enzymatic N-deethylization of the diethylamide radical on the LSD side chain (position 8). M2 was identified as nor-LSD, a N-demethylated degradation product.

In further *in vitro* experiments, it was shown that 1 mole LSD was metabolized into 1 mole 2-oxy-LSD by the NADH-dependent microsomal enzyme system (Axelrod *et al*., 1957; Freter *et al*., 1957). Oral administration of 2-oxy-LSD (300 µg) in humans showed no effect in comparison with 30 µg LSD (Axelrod *et al*., 1957).

Klette *et al*. (2000) analysed the metabolization of LSD into 2-oxo-3-hydroxy LSD (O-H-LSD) in human liver microsomes and in hepatocytes *in vitro*. Phase 1 of the substance metabolism was measured by the microsomes' incubation with 30 mg LSD; the hepatocytes' metabolism was measured with 1 µg LSD at different times using liquid chromatography and mass spectrometry. O-H-LSD was identified in both incubated fractions, whereby the resulting amount of O-H-LSD growth is dependent on time. O-H-LSD could be detected neither in samples without LSD treatment nor in LSD samples without microsomes or hepatocytes. This proves that O-H-LSD is a metabolite in human liver microsomes and hepatocytes. A hitherto unidentified metabolite was identified as dihydroxy-LSD by 'mass spectral interpretation'.

Canezin *et al*. (2001), on studying human urine following intake of street-LSD, (using electrospray ionization tandem mass spectrometry) discovered lysergic acid ethyl-2-hydroxyethylamide (LEO) and trioxylated LSD besides LSD, norLSD, LAE, 2-oxo-LSD, O-H-LSD, and 13/14-hydroxy-LSD glucoronides.

The main metabolite in the urine was O-H-LSD, which could not be detected in blood plasma of two test persons.

Metabolism inhibition

Chlorpromazine and SKF 525 (an inhibitor of hepatic monooxygenase) were tested as inhibitors of LSD metabolism *in vitro*. Chlorpromazine prolongs the biological half-life in mice from 7 to 15 min, just as did SKF 525-A, almost completely blocking the enzymatic transformation of LSD, as well *in vitro* as *in vivo*, even in tiny amounts. The fact that SKF 525-A already completely inhibited the enzymatic dealkylation in concentrations of 10^{-3} M led to the conclusion that LSD was transformed by NADPH-attached microsomal enzymes (Axelrod *et al*., 1957).

Excretion

According to early studies, the excretion of LSD proceeds via liver and gall bladder into the duodenum (Stoll *et al*., 1955), thus the largest percentage is excreted unchanged along with the faeces and only a small fraction is detectable as metabolites in urine.

After intravenous administration of ^{14}C-LSD in rats, a bile duct puncture was conducted, and the bile acid was collected for 3 h. As much as 64% of the radioactive dose could be identified, while 12% was located in the content of the intestinal tract (Boyd *et al*., 1955a). The contents of one LSD-treated rat's gall bladder was led into the lower part of another rat's gastrointestinal tract. Only around 1% of the dose appeared in the other rat's blood. Since another, similar experiment showed the same results, it was presumed that the radioactive components excreted by the gall bladder could not be reabsorbed in the intestine (Boyd, 1959).

In a further excretion experiment, rats were administered with ^{14}C-LSD (1 mg/kg i.p.). Thereof, 7% was excreted, half of it in the exhaled air, the other half in faeces and urine. After 12 h, 8.5% of the dose was located in the gastrointestinal tract and almost 50% in the intestine. In rats, more than 70% of the radioactive LSD was located in the gastrointestinal tract (Boyd *et al*., 1955a; Boyd, 1959). After 60 h of collecting, the animals' urine exhibited 8% and the faeces 80% of the LSD (Boyd, 1959).

In monkeys, less than 1% of the administered LSD could be detected in urine and faeces after 48 h (Axelrod *et al*., 1957).

When searching for aromatic urine metabolites after LSD intake in humans (open, crossover, $n = 23$, 1 µg/kg, p.o.) by means of semi-quantitative paper chromatography, a significantly reduced excretion of phenolic acids was detected (Masuda & Dorpat, 1960).

In order to follow up possible changes of indole metabolism after LSD intake, test persons were given LSD (open, $n = 8$, 100 µg, i.v.), and results compared to controls. Tryptamine was not detectable in chromatograms. The excretion of indole acetate, however, was elevated by 24% (Vasconetto, 1965).

Elimination half-life

The calculation of the elimination constants resulted in a LSD half-life of 37 min in mice (Lanz *et al*., 1955), 130 min in cats, and 100 min in macaques (Axelrod *et al*., 1957). In animals, the half-life of LSD in plasma correlated quite accurately to the decline of behavioural changes, as to the gradual disappearance of the substance from brain (Freedman & Coquet, 1965).

Based on their collected data, Aghajanian and Bing (1964) calculated the half-life of LSD ($n = 5$, 2 µg/kg, i.v.) as being 175 min in humans. Subsequent pharmacokinetic analyses led to the conclusion that the plasma concentration of LSD could be explained best in an open two-compartment model. For instance, changes in the performance score correlated strongly with the LSD concentration in tissue (outer compartment), said to account for 11.5% of body weight. Thus, the elimination half-life of LSD in plasma is around 103 min (Wagner *et al*., 1968).

Dosage

The minimal effective dose of LSD that evokes measurable psycho-vegetative effects is about 20–30 µg. Smaller doses lead to only faintly measurable changes (Stoll, 1949; Greiner *et al*., 1958). The half-maximal effective concentration (EC_{50}) however varies strongly between individuals, because the sensibility to a dose of 100 µg clearly varies. About 10% of a population does not notice any subjective changes, while the majority reports distinguishable psychic alterations (Cohen, 1967). Abramson *et al*. (1955a–e) tested different doses of LSD on 31 healthy subjects and noticed a dose-dependent correlation between psychotic symptoms and changes in perception. The test subjects in studies by De Maar *et al*. (1960) could distinguish among doses of 25, 50, and 100 µg LSD since the symptoms seemed to be dose-dependent. Hoffer (from Hoffer & Osmond, 1967) observed the identification of different doses of LSD by healthy subjects themselves, in double-blind trials. The test subjects were not able to notice 15 µg LSD, whereas 25 µg was noticed by the majority. Klee *et al*. (1961) also asserted a linear dose–response relationship of between 1 and 16 µg/kg.

Detection in body fluids

For the detection of LSD in body fluids (mainly serum and urine), one has to differentiate between screening methods (high sensitivity) and confirmation analyses (high specificity). Screening analyses are carried out by means of

radioimmunoassay or immunoassays. By contrast, chromatographic methods allow the confirmation and, where applicable, a quantification (Wölfel, 2001).

In addition, it is to be pointed out that the LSD-metabolite O-H-LSD is present in a 16- to 43-fold higher concentration than LSD in urine samples and can be detected by liquid chromatography-mass spectrometry (e.g. Cai & Henion, 1996; Von Bocxlaer *et al*., 2000).

Pharmacodynamics

The neuropharmacology of LSD is complex and neither completely clarified nor understood. Indeed, it has been known from early on that LSD has a high affinity for the binding sites of neurotransmitters (serotonin, dopamine, and noradrenaline receptors) (Closse *et al*., 1984), but the complex and partly contradictory effects on these transmitter systems are to a great extent not understood (cf. Winters, 2008; Nichols, 2004).

The variety of LSD's biological effects is reflected in its interactions with a multitude of receptors.

Serotonin receptors

Due to molecular similarities between LSD and serotonin, early studies already addressed the hypothesis that LSD exerts hallucinogenic effects by modulating the serotonin system in the CNS (Gaddum & Hameed, 1954; Woolley & Shaw, 1954a,b). A dose-dependent reduction of the activity of serotonergic neurons is observable after LSD administration (e.g. Haigler & Aghajanian, 1974; Jacobs & Trulson, 1979). This however, was immediately called into question when it was discovered that an LSD bromine derivative, 2-bromine-lysergic acid diethylamide (BOL-148), possesses an equally strong anti-serotonergic potency, while not evoking LSD effects (Cerletti & Rothlin, 1955; Rothlin, 1957a). Based on the following explanations it will become clear that LSD acts in a complex manner, as agonist, partial agonist, and also as antagonist on different serotonin sub-receptors (Table 2.6).

LSD increases the serotonin level in the CNS (Freedman, 1961) and lowers the concentration of the serotonin metabolite 5-HIAA (5-hydroxy-indole-acetic acid; Rosecrans *et al*., 1967), implying that LSD lowers the serotonin turnover in the brain. A further observation was made by Aghajanian *et al*. (1968), showing that a systemic LSD application *in vivo* causes a considerable decrease of the spontaneous activity of serotonergic neurons in the dorsal and median raphe nuclei.

Anden *et al*. 1968 were the first to suspect LSD's direct agonistic effect on serotonin receptors in the brain. Molecular biological data show that a large

Table 2.6 Localization and LSD-specific functions of some 5-HT-receptor subtypes

Receptor	Localization	Function	LSD effect	Effects on physiology
5-HT_{1A}	Raphe nuclei (pre- and post-synaptic), hippocampus, neocortex	Negative feedback inhibition	Agonism	Inhibition of raphe activity —> diminished serotonin release
5-HT_{1C}	Unknown	Modulation of 5-HT_2-receptor function	Partial agonism	Increase of phosphoinositol hydrolysis
5-HT_{2A}	Neocortex, claustrum, nucleus accumbens, nucleus facialis, and tractus solitarius (post-synaptic)	Manifold		Manifold
	Nucleus reticularis	'Gate' for sensory signals to the cortex	Partial agonism	
	Corticale pyramidal cells	Activation of cortical NMDA-receptors		Increase of glutamate concentration
5-HT_{2C}	Plexus choroideus	Unknown	Agonism	Increase of phosphoinositol hydrolysis

group of different 5-HT receptor subtypes (and species-specific subtypes) exists. Most subtypes exert their properties via G-protein-mediated reactions (Table 2.7).

The 5-HT_2-receptor family

5-HT_{2A} receptors The brain's own 5-HT_{2A} receptors are usually situated in the prefrontal cortex and in the claustrum, the nucleus accumbens, the nucleus facialis, and in the tractus solitarius. The highest density is found in the lamina IV (Pazos *et al*., 1985a). The 5-HT_2 receptors are found prevalently in the post-synaptic regions.

Based on animal and human testing, a stimulation of the 5-HT_2 receptor subtype has been assumed since the 1990s, as the cause of the relatively uniform behavioural changes (Glennon, 1990; Glennon *et al*., 1992). This theory is based on the fact that many hallucinogens bind to 5-HT_2 receptors with high affinity (Glennon *et al*., 1984; Titeler *et al*., 1988; Pierce & Peroutka, 1989; Pierce *et al*., 1992).

Glennon *et al*. (1983a) showed that in rats, 5-HT_2 antagonists (ketanserine and pirenperone) block the effects of hallucinogens (phenethylamine and tryptamine derivatives) (Colpaert *et al*., 1982; Leysen *et al*., 1982; Colpaert & Janssen, 1983), which implied agonistic activity. Some years later, Pierce and Peroutka (1988) concluded on the basis of their studies that the effects were 'not derived from direct activation of 5-HT_2-receptors'. The authors rather assumed there was an antagonistic effect on 5-HT_2 receptors.

[^{3}H]-LSD has often been used in autoradiography. It binds with high affinity on different types of receptors in the CNS (Diab *et al*., 1971; Gatzke, 1977; Meibach *et al*., 1980; Palacios *et al*., 1983). McKenna and Saavedra (1987) analysed the binding of (+)-[^{125}I]-2-iodine-LSD in rat brains. There was a high binding affinity observable in the cortex and in other brain regions (also Engel *et al*., 1984; Nakada *et al*., 1984). According to this, LSD acts in the

Table 2.7 5-HT-receptor subtypes (from Hüther & Rüther, 2003)

G-protein-coupled receptors	
5-HT_1-'family'	5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{1F}, 5-HT_{dro1}, 5-HT_{dro2A}, 5-HT_{dro2B}, 5-HT_{snail}
5-HT_2-'family'	5-HT_2, 5-HT_{1C}, 5-HT_{2F}
Others	5-HT_{5A}, 5-HT_{5B}, 5-HT_6, 5-HT_7
Ligand-mediated ion channel	5-HT_3
Transporter	5-HT-outside

cortex, primarily via 5-HT_{2A}-receptors (Pompeiano *et al.*, 1994; Wright *et al.*, 1995).

The nucleus reticularis of the thalamus is of special relevance, due to its function as a kind of 'gateway' for signals to the cortex. Neuronal influences on the nucleus reticularis derive from other thalamus nuclei and run back to the thalamus as inhibitory projections. The nucleus reticularis ultimately controls the intensity and quantity of the signals entering the thalamus by a negative feedback mechanism, which allows for a selective attentiveness to relevant sensory impulses (Crick, 1984; Sherman & Guillery, 1996).

In this context, there are two noteworthy [^{18}F]-FDG-PET studies in which test subjects were given psilocybin, a hallucinogenic substance similar to LSD. One study showed a significant rise in the glucose metabolism in the thalamus (Vollenweider *et al.*, 1997), while Gouzoulis-Mayfrank *et al.* (1999) found a metabolic *decline* in the right thalamus and parts of the left thalamus. Thus, Vollenweider's (2001) plausible hypothesis that 'opening of the thalamic filter by hallucinogens' leads to their psychosensory effects could not be verified.

In addition, studies point to the fact that hallucinogenic tryptamines (LSD, psilocybin, DMT) act more as partial agonists than as antagonists on 5-HT receptors (Meltzer *et al.*, 1982; Marek & Aghajanian, 1996; Vollenweider *et al.*, 1998).

The locus coeruleus and also the raphe nuclei belong to a well-definable group of nucleus regions of the formatio reticularis with predominantly noradrenergic neurons. The largely inhibitory projections of these cell groups are dispersed widely across the CNS and control the onward transfer of sensitive afferents. Thus, the locus coeruleus is seen as a nodal point for the registration of changes in the inner and outer 'world'. Some authors suppose that this central region plays a special role in functional brain changes under the influence of hallucinogens (Cedarbaum & Aghajanian, 1978; Aston-Jones & Bloom, 1981). Since their effects on the locus coeruleus is inhibited by selective 5-HT_{2A} antagonists (e.g. ketanserine), one can assume that there is a 5-HT_{2A}-mediated mechanism behind it (Rasmussen & Aghajanian, 1986; Gorea & Adrien, 1988). However, it is to be assumed that LSD does *not directly* act on the locus coeruleus. If LSD is applied via micro-iontophoresic manipulations into cells of the adrenergic nucleus region, they do not trigger any effects (Aghajanian, 1980).

Visceral motor neurons in rat brains were not significantly influenced by LSD (100 mmol/l) in terms of input resistance and membrane potential, although it increased the electrical excitability of the cells (Aghajanian, 1994). Garratt *et al.* (1993) observed an amplification of the unspecific cation stream I_h by serotonin, after a raise in excitability in visceral motor neurons.

Interestingly, LSD constitutes a greater amplification of I_h than serotonin itself. This amplification can be inhibited by both 5-HT2/5-HT1A antagonists (Spiperone) and by 5-HT_2/5-HT_{1C} antagonists (Ritanserine), implying a 5-HT_2-mediated rise of I_h.

Effects on the cortical glutamate In the past few years, clues have been found that point to a rise in cortical glutamate triggered by hallucinogens, which occur through the activation of 5-HT_{2A} receptors. The highest density of mGlu2/3 receptors is to be found in the prefrontal cortex in Lamina I and Va, correlating with the dispersion of 5-HT_{2A} receptors in the cortex (Marek *et al.*, 2000).

Arvanov *et al.* (1999a, 1999b) developed the hypothesis that the glutamate modulation could be an important mechanism of action in psychoactive substances (cf. Aghajanian & Marek, 1997; Marek & Aghajanian, 1998). They also report a gradually appearing 5-HT_{2A}-mediated inhibitory effect of LSD on *N*-methyl-D-aspartate (NMDA)-receptor-induced neurotransmission in pyramidal cells. This also speaks for a 5-HT_{2A}-mediated pre-synaptic glutamate release. However, the LSD concentration necessary for an amplifying effect (500–2000 nM) is physiologically irrelevant. By contrast, the IC_{50} values for blocking the NMDA-mediated effects with (9 nM) LSD are situated in the relevant physiological range.

Studies with antagonists revealed that the inhibitory activity is triggered by a Ca^{2+}/CaM-KII-dependent signal transduction mechanism (Nichols, 2004).

5-HT_{2A}-mediated reactions 5-HT_2 receptors are interconnected with a second messenger system with phosphatidyl inositol. The phosphatidyl inositol turnover is stimulated by serotonin and inhibited by antagonists of the 5-HT_2 receptor. As a partial agonist, LSD stimulates the hydrolysis of phosphatidyl inositol in the frontal cortex and plexus choroideus, which points to the activation of a 5-HT_{2A}- and 5-HT_{2C}-receptor-associated second messenger system (Sanders-Bush & Breeding, 1988; Sanders-Bush *et al.*, 1988; Burris *et al.*, 1991).

In nanomolar concentrations, LSD does not *directly* stimulate the phosphatidyl inositol turnover; however, it inhibits the stimulating effects of serotonin (10^{-5} mol/l) (Pierce & Peroutka, 1988; Sanders-Bush *et al.*, 1988). This implies a partial agonistic activity of LSD on the 5-HT_{2A} receptors (with 25% effectiveness of serotonin) (Monte *et al.*, 1997; Kurrasch-Orbaugh *et al.*, 2003b).

Sadzot *et al.* (1989) flagged 5-HT_2 receptors in samples of human cerebral cortex with [^{3}H]-ketanserin and demonstrated that the addition of LSD acts as an agonist on this receptor.

During the generation of hypothermia in rats, a 5-HT_2-mediated mechanism was described, which can be inhibited by 5-HT_2 antagonists (e.g. Gudelsky *et al.*, 1986; Aulakh *et al.*, 1994; Mazzola-Pomietto *et al.*, 1995).

Down-regulation of receptors and development of tolerance The chronic application of LSD leads to a down-regulation of 5-HT_2 receptors, so that the tolerance development towards LSD was thought to be related to this. However, there is no down-regulation of post-synaptic 5-HT_{1A} receptors (Buckholtz *et al.*, 1985; 1988; 1990). The potent hallucinogen DMT leads neither to a down-regulation of 5-HT_2 receptors (Smith *et al.*, 1998) nor to the development of tolerance (Strassman *et al.*, 1996).

5-HT_{2A} receptor activation and gene expression LSD also has an influence on gene expression (Dragunow *et al.*, 1989), which in turn can lead to changes in neuronal functions. Nichols and Sanders-Bush (2002) analysed these changes in rats.

After 90 min the application of LSD (1 mg/kg, i.p.) leads to the expression of *c-fos a*nd *arc*. Furthermore, the authors proved the existence of serum glucocorticoid kinase (*sgk*), *I*κβ-α, neuron-derived orphan receptor 1 (*Nor1*), *ania3*, and *krox-20*. Among the analysed genes, *arc* stuck out the most; its expression in the prefrontal cortex was raised fivefold by the administration of LSD. The increased *ania3*-expression also seems to be of importance, since this gene plays a role in the glutamate system, which, in turn, plays an important part in the mechanism of effect in hallucinogens.

Moreover, Nichols *et al.* (2003) analysed the effects' dependence on time and dose on the genes concerned. They used 5-HT_{1A} and 5-HT_{2A} antagonists in order to identify the (LSD-activated) receptors that mediated the changes in gene expression in the prefrontal cortex. Most transcripts displayed their maximal concentration after 90 min, but the 'early' genes (like *c-fos*) were significantly elevated after 45 min. After 5 h, the values dropped to the original level, with the exception of *Nor1*. The highly selective 5-HT_{2A} antagonist M 100.907 inhibited the elevated expression of the genes under investigation (with the exception of *sgk* and Iκβ-α). It is worth noting that almost all the genes influenced by LSD are of importance to the synaptic transfer processes.

Gonzalez-Maeso *et al.* (2003) quantified the concentration-dependent changes in gene expression in reaction to different 5-HT_{2A} agonists in HEK293 cells that express human 5-HT_{2A} receptors. Then, in 5-HT_{2A}-receptor knock-out mice, they observed whether the LSD-induced changes could be traced back to the 5-HT_{2A} receptor. Three genes were formed more frequently after LSD administration: *egr-1* > *egr-2* > *period-1* (Nichols & Sanders-Bush, 2002).

The clearest changes were observed at *egr-1* which, amongst others, regulates the expression of cellular signal proteins (Liu *et al*., 1996). LSD raises the expression of *egr-2*, also known as *krox-20*. The third gene is *period-1*, a gene acting in the circadian regulation (Cermakian *et al*., 2001). Both Nichols and Sanders-Bush (2002) and Gonzalez-Maeso *et al*. (2003) detected a raised gene expression of *I*κβ-α. Even in 5-HT_{2A} receptor knockout mice, the expression of this gene was enhanced, pointing to mediation by another receptor type. Nichols and Sanders-Busch (2004) also discovered an increased expression of C/EBP-beta (transcriptions factor) in mitogen-activated protein kinase (MKP-1) and ILAD-1 (acts in the processing of light stimulation in the human eye) after LSD administration in the pre-frontal cortex in mammals.

5-HT_{1C} receptors The 5-HT_{1C} receptor also belongs to the 5-HT_1 receptor family and is also associated with a phosphoinositol second messenger system too. In this system, LSD acts as a partial agonist. It can cause up to 34% of the effect of serotonin.

Hoyer *et al*. (1986) report that LSD binds with high affinity to 5-HT_{1C} receptors in the plexus choroideus of pigs.

In relation to radioligand binding, substances like LSD do not interact as specifically as DOM (2,5-dimethoxy-4-methylamphetamine), DOB (2,5-dimethoxy-4-bromoamphetamine), or DOI (2,5-dimethoxy-4-iodoamphetamine). As discussed above, some of the effects of LSD can be explained by its partial agonistic activity. This means that LSD is 'an high-affinity, low-efficacy nonselective 5-HT agonist' (Glennon, 1990). In the absence of other agonists, LSD acts as an agonist, but in the presence of a highly effective agonist, it acts as an antagonist.

In general, many of the effects of LSD or indole alkyl amines follow a biphasic course that could be explained by a functional auto-antagonism at the 5-HT_1 receptor. Hence, Glennon (1990) assumes a controlling or modulating function of the 5-HT_1 receptor in interaction with 5-HT_2 receptors.

5-HT_{2C} receptors The 5-HT_{2C} receptor's role in the action of hallucinogenic substances could not be clarified to date, for there is no known hallucinogen with an affinity to the 5-HT_{2C} receptor that does not at the same time activate the 5-HT_{2A} receptor (Sanders-Bush, 1994; Fiorella *et al*., 1995b/c).

Interactions with receptor sites of different brain regions

In the previous chapter a range of potential mechanisms that have an influence on LSD's mode of action were presented. These interactions of components are, however, much harder to analyse and discuss. Nonetheless, an attempt to outline a cursory synopsis will be made in the following section.

In an intact animal organism, the application of hallucinogenic substances leads to a suppression of the raphe nuclei activity through the activation of 5-HT_{1A} receptors and to an indirect stimulation of inhibitory GABA neurons (Liu *et al.*, 2000), with only slight to no activation of cortical 5-HT_{1A} or 5-HT_{2A} receptors. After systemic application of hallucinogenic substances, local concentrations of 5-HT_{2A} agonists stimulate HT_{2A} receptors of pyramidal cells in the cortex. Hallucinogens also stimulate excitatory 5-HT_{2A} receptors on glutaminergic axons of the thalamus (which may also be due to an as yet unspecified, indirect mechanism). The consequent effects would be an enhanced excitability of cells in the cortical pyramidal and a glutamate release in cortical neuron regions (Martin-Ruiz *et al.*, 2001; Nichols, 2004). Since mediodorsal thalamic projections normally react to sensory input 'processed' in the thalamus, the effects of hallucinogenic substances (in the presence of sensory stimuli) on these terminals would lead to release of glutamate. As a consequence, the pyramidal cells would be hyper-excitable, thus additionally increasing the effects of extracellular glutamate.

The effect of hallucinogenic substances on the function of the thalamus, notably on its nucleus reticularis, has so far not been accounted for sufficiently. The activation of 5-HT_{2A} receptors in thalamus nuclei can lead to a considerable modulation of sensory processes. In particular, the nucleus reticularis interacts—due to its inhibitory GABAergic input—directly with the other thalamus nuclei and thus can contribute to the selection of sensory information (Smythies, 1997; Behrendt, 2003). In a tonic mode, the activity of thalamic relay cells is dependent on the respective afferent input, while in the 'burst-firing' mode sensory messages are not effectively transferred (McCormick & Feeser, 1990). The inhibitory input of the nucleus reticularis hyperpolarizes thalamic relay cells and in that way can transform the reaction mode into the 'burst-firing' mode, thus preventing the activity threshold being reached through an accumulation of sensory inputs. As mentioned before, 5-HT_{2A} receptors can activate inhibitory GABA interneurons, leading to the assumption that 5-HT_{2A} receptor activation in the nucleus reticularis enhances the inhibitory input going to relay cells. A dysfunction of the nucleus reticularis thus would lead to an absence of the specific sensory inhibition of certain thalamus nuclei and an impairment of the 'signal-to-noise' relation. This 'noise' could then dominate the stimulus-specific activity, and the relay cells, without adequate sensory input, would be incorporated in thalamocortical circuits (cortico-striato-thalamo-cortical (CTSC) loops, after Vollenweider & Geyer, 2001). In that way, the combination of increasingly excitable thalamic relay cells and the dysfunction of the nucleus reticularis could lead to the activation of thalamocortical loops and to a formation of connected associations of

thalamocortical oscillations. These signals, independent of afferent inputs, could in turn potentially generate modified perceptions (hallucinations or dreams) (Behrendt, 2003).

Vollenweider and Geyer (2001) presume that hallucinogens block the information-digesting process of a CSTC feedback mechanism system (Figure 2.8). It could be that this leads to an inability to select specific information and to focus attention so that it meets the requirements of everyday life. They postulate that non-physiological disconnections of the filter mechanism responsible for sensory and cognitive information lead to an 'overload' of the cortex's capacity to process these influences. In addition, they say that hallucinogens change the thalamocortical transmission through stimulation by 5-HT_{2A} receptors found in numerous components of the CSTC (prefrontal cortex, striatum, nucleus accumbens, and thalamus). These considerations, however, are modified by the deliberation that hallucinogens seemingly induce a direct and massive pre-synaptic glutamate release from afferent nerves in the thalamus, thus constituting the equivalent of the 'sensory overload' in the cortex, which exists independently from the amount of information arriving in the thalamus at that moment.

Based on the fact that almost all hallucinogens prove a somewhat higher affinity to 5-HT_{2C} than to 5-HT_{2A}-receptors, it remained unclear for a long time which sub-receptor type is decisive for the mechanism of effect. As mentioned before, in the cortex, where LSD is principally supposed to operate, mainly 5-HT_{2A} receptors are found (Pompeiano *et al.*, 1994; Wright *et al.*, 1995). Moreover, Kurrasch-Orbaugh *et al.* (2003a) calculated that the EC_{50} of LSD, in order to activate the 5-HT_{2A} receptor, is identical to the maximum plasma level of LSD (10–20 nM) after i.v. or p.o. application (Aghajanian & Bing, 1964).

5-HT_{1A} receptors

5-HT_{1A} receptors are situated in the raphe nuclei on the somata of serotonergic neurons (Sotelo *et al.*, 1990). They act in the degeneration and occur both in the pre- and post-synaptic regions. Post-synaptic 5-HT_{1A} receptors are also located in other regions of the brain, such as the hippocampus, where affects and emotions are modified (Hamon *et al.*, 1990).

LSD (like hallucinogens 5-MeO-DMT and psilocin) has a high affinity to the 5-HT_{1A} receptor (McKenna *et al.*, 1990; Blair *et al.*, 2000).

Therefore, Aghajanian (1994) asked the question as to why LSD can be effective if it works almost exactly like an endogenous neurotransmitter. He presumes that this might be due to its larger effectiveness as an agonist on somatodendritic 5-HT_{1A} receptors (compared with post-synaptic 5-HT_{1A} receptors) (Haigler & Agajanian, 1974; Aghajanian & Haigler, 1975).

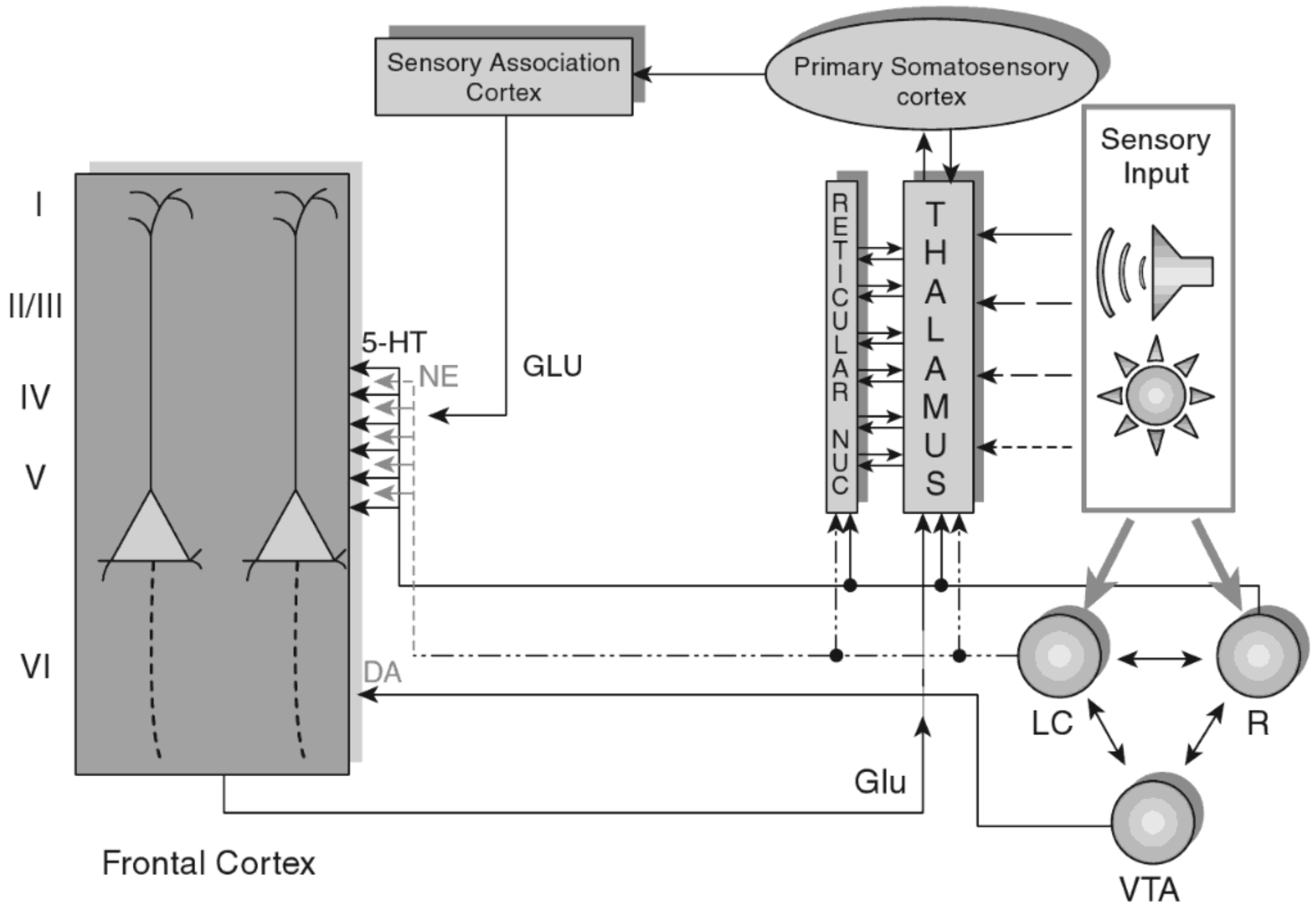

Fig. 2.8 A simple diagram of possible interactions between brain areas that are affected by 5-HT_{2A} agonist actions of hallucinogens. In PFC, 5-HT_{2A} receptors are localized on the proximal portion (deep layer IV/superficial layer V) of apical dendrites and dendritic spines on pyramidal cells. R (raphe nucleus) sends serotonin projections to all forebrain structures, including the frontal cortex. Hallucinogens reduce firing of raphe cells either directly by stimulation of 5-HT_{1A} receptors or indirectly by 5-HT_{2A} receptor activation of inhibitory GABA interneurons. Cessation or reduction of raphe cell firing would lead to a disruption of normal serotonergic tone, which would include reduced activation of inhibitory 5-HT_{1A} receptors on cortical pyramidal axons. Essentially, all incoming sensory information is processed through the thalamus, with modulation by the reticular nucleus of the thalamus, which has afferents from specific thalamic nuclei and associated cortical areas. Many thalamic nuclei as well as the reticular nucleus express 5-HT_{2A} receptors. Alterations in the firing mode of thalamic neurons are associated with dramatic changes in the neuron's responsiveness to peripheral stimuli (McCormick & Bal, 1997). Both LC and VTA express 5-HT_{2A} receptors and receive input from the raphe. The LC sends noradrenergic projections to both thalamus and cortex. Hallucinogens potentiate burst-firing in LC neurons in response to novel stimuli. Stimulation of a1-adrenergic receptors in cortex depolarizes pyramidal cells and appears to share a common Gq-coupled PLC pathway with 5-HT_{2A} receptors. VTA cells are depolarized by activation of 5-HT_{2A} receptors, which would potentially lead to enhanced release of DA in cortex. There is extensive evidence that a significant portion of 5-HT, NE, and DA release in the cortex may have effects on cortical neurons through volume transmission rather than direct synaptic connections (from Nichols, 2004, p. 71).

Among the 5-HT_1 receptors, LSD has the highest affinity to 5-HT_{1A} and 5-HT_{1D} subtypes. On 5-HT_{1A} receptors, LSD acts as a full agonist (Penington & Fox, 1994). Parallel to this, there are also indications for agonistic effects on autoreceptors (Gallager & Aghajanian, 1975).

Histological analyses show that the units inhibited by LSD are localized at dorsal and medial raphe nuclei. Since LSD was administered parenterally, either a direct or an indirect mechanism could be responsible for that inhibition (Foote *et al.*, 1969). Some authors presume that LSD has a serotonin-equivalent effect on the post-synaptic receptors of serotonergic neurons, resulting in a feedback inhibition of the raphe nuclei (Aghajanian & Freedman, 1968; Aghajanian *et al.*, 1968; Anden *et al.*, 1968). However, other studies showed a blocking of the reactions to serotonin in raphe nuclei after iontophoretic LSD application (Bloom *et al.*, 1964; Bradley & Wolstencroft, 1965; Phillis & Tebecis, 1967; Roberts & Straughan, 1967).

Nielsen (1985) observed that ketanserine and pirenperone could not block the LSD-specific behaviour in trained monkeys ($n = 4$, 0.06 mg/kg, s.c.).

While the stimulation of pre-synaptic 5-HT_{1A} receptors does not seem to be sufficient to cause hallucinations, the activation of these receptors combined with 5-HT_2 receptors could be accountable for the creation of hallucinogenic LSD effects. This is supported by animal models, in which the LSD effects are nullified by a combined administration of the 5-HT_{2A}/5-HT_{2C} receptor antagonist ritanserin and the 5-HT_{1A} antagonist propranolol (Mittman & Geyer, 1989, 1991). In addition, there are hints to a functional interaction of 5-HT_{1A} and 5-HT_{2A} receptors (Arnt & Hyttel, 1989).

There is also evidence that pre-synaptic 5-HT_{1A} receptors do not play a special role in the region of the raphe nuclei with respect to hallucinogenic LSD effects. For example, the effects on the behaviour of different species outlast the changes in the raphe nuclei. In addition, these structures are still receptive to LSD effects even when tolerance has been developed (Haigler & Aghajanian, 1973).

The 5-HT_1 receptor subgroups' role can be summarized as follows: through the inhibition of serotonergic neuron activity by somatodendritic 5-HT_{1A} receptors and stimulation of inhibitory pre-synaptic 5-HT_{1B} autoreceptors, LSD reduces the tonic release of serotonin to post-synaptic neurons. However, since LSD acts only weakly as agonist at the post-synaptic 5-HT_{1A}-receptor, it might exert its primary post-synaptic effect at the 5-HT_2 or 5-HT_{1C} receptor (Aghajanian, 1994).

5-HT_{1D} receptor LSD has a binding affinity to the human terminal 5-HT_{1D} autoreceptor that is comparable to the affinity for 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptors. The 5-HT_{1D} receptor is situated in the basal ganglia and in the substantia nigra on the pre-synaptic terminals of serotonergic neurons;

it serves degeneration. Hitherto, hardly anything has been established about the effects of LSD on this receptor (Hoyer, 1989).

Other 5-HT receptors LSD has only a minor nanomolar affinity to the subtypes of serotonin receptors that have been identified more recently (5-HT_{5a}, 5-HT_{5b}, 5-HT-$_6$, 5-HT_7, 5-HT_{1E}) (Erlander *et al.*, 1993; Lovenberg, 1993a; 1993b; Monsma *et al.*, 1993). In general, the knowledge concerning these receptors has been meagre to date.

Interactions of LSD and serotonin re-uptake inhibitors (SSRIs)

When LSD acts on 5-HT_2 and 5-HT_{1A} receptors, their down-regulation ought to weaken the effects of LSD. It has been long known that a long-term effect of many antidepressants is to reduce the number of 5-HT_2 receptors in different regions of the brain (Heninger & Charney, 1987; Murphy *et al.*, 1987). However, some studies (after chronic application of fluoxetine) show a reduction in the number of receptors in rat brains (Stolz *et al.*, 1983; Wamsley *et al.*, 1987), while others indicate an increase (Dumbrille-Ross & Tang, 1983; Klimek *et al.*, 1994). After long-term application of citalopram (de Montigny *et al.*, 1990) or zimelidin (Blier & de Montigny, 1983), reduction in the activity of dorsal raphe neuron (which normally appears after LSD i.v.) is blocked, which can be evaluated as the down-regulation of 5-HT_{1A} autoreceptors (Moret & Briley, 1990a/b). There is evidence that intake of SSRIs attenuates LSD effects in humans (Bonson *et al.*, 1996).

Dopamine receptors

LSD has a moderate binding affinity to post-synaptic dopamine receptors (Creese *et al.*, 1975; Burt *et al.*, 1976). At the same time, LSD shows antagonistic effects towards dopamine (Pieri *et al.*, 1974).

Radio receptor studies showed that LSD has a high binding affinity to dopamine receptors (Burt *et al.*, 1976; Creese *et al.*, 1976).

Stolk *et al.* (1974), however, detected no significant changes in the [^{3}H]-dopamine concentration 1 h after LSD application (1300 µg/kg); Persson (1970) merely found an accumulation of [^{3}H]-dopamine in the nucleus caudatus region 30 min after 2 mg/kg LSD. Christoph *et al.* (1977) observed a 78% decrease in the activity of dopaminergic neurons after LSD administration (25–50 µg/kg, i.v.) in the substantia nigra of rats. Haloperidol (0.1 mg/kg) inhibited these LSD effects.

Accepting this, LSD is a dopamine agonist in the CNS (Christoph *et al.*, 1977).

Da Prada *et al.* (1975) detected no influence of LSD (0.2 mg/kg, i.p.) on the concentration of dopamine in rats.

Hollunger and Persson (1975) analysed the effects of LSD (0.1–4.0 mg/kg, i.p.) on the DOPA concentration in rat brains, after the i.p.-injection of 100 mg/kg NSD1015 (decarboxylase inhibitor). There was a dose-dependent augmentation of the DOPA accumulation in the brain (Figure 2.9).

Persson and Johansson (1978) analysed whether the boost of DOPA after LSD administration (0.5 mg/kg, i.p.) resulted from activation of the dorsal or medial raphe nuclei. Only a combined lesion of both nuclei inhibited the effect of LSD.

Persson (1978) could not find any proof of LSD (0.5 mg/kg, i.p.) affecting DOPA accumulation in the striatum, and only a 7% increase in the telencephalon 135 min after LSD administration.

Kehr and Speckenbach (1978) observed a dose-dependent increase in dopamine synthesis after LSD administration (50 µg/kg–5 mg/kg) (Smith *et al.*, 1975).

Some investigators were engaged with the influence of LSD on the adenylate cyclades (Spano *et al.*, 1975; Ahn & Makman, 1979). Von Hungen *et al.* (1974) found that LSD can activate adenylate cyclase and at the same time act as an antagonist in the stimulation of this enzyme through serotonin. LSD acts both

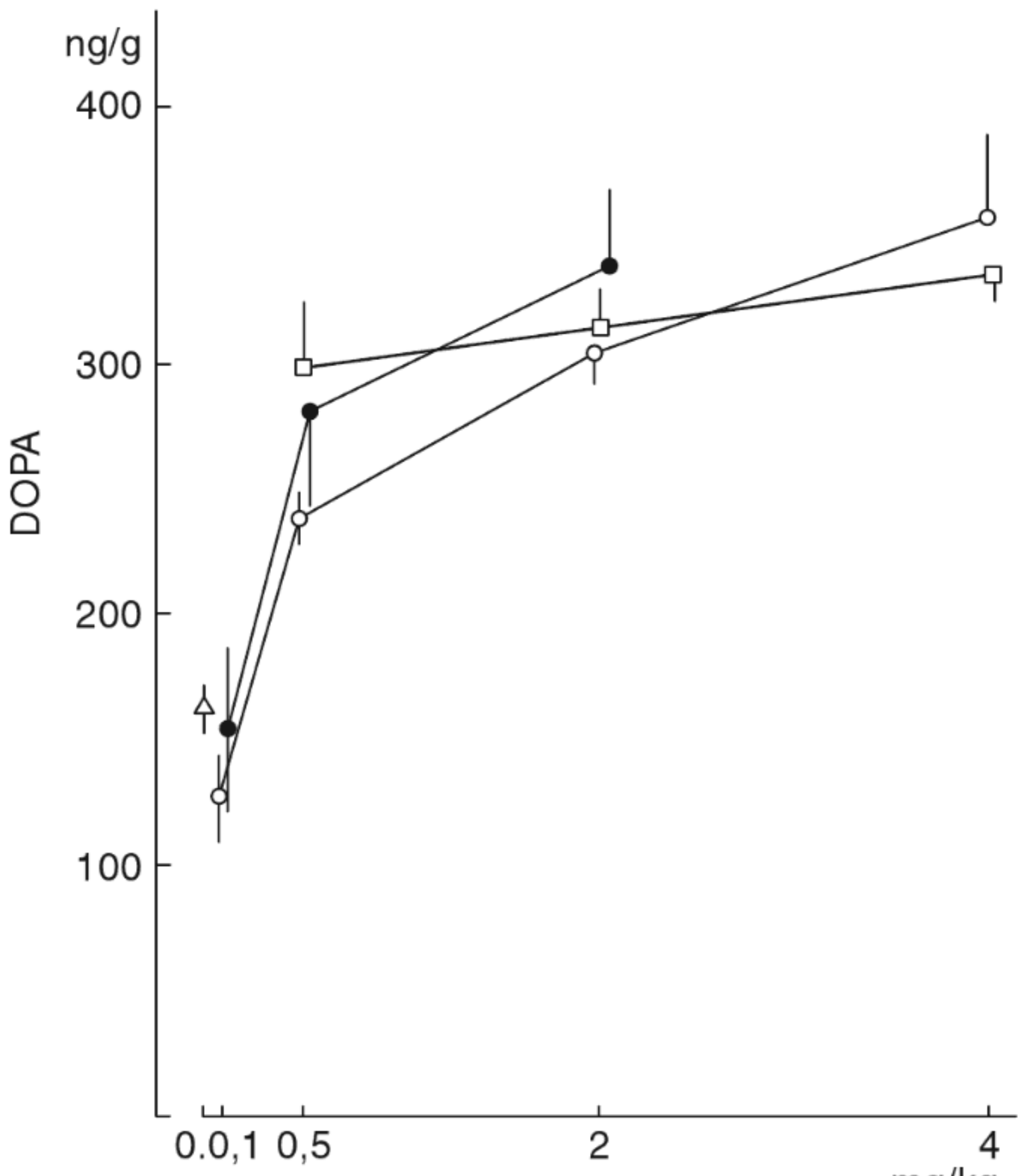

Fig. 2.9 DOPA accumulation in rat brain after i.p. injection of NaCl (Δ), LSD (o), BOL-148 (•), and haloperidole (❑) (Hollunger & Persson, 1975, p. 157).

as dopamine agonist and as an antagonist on dopamine receptors in the brain, in the rat preparations used in this experiment.

In a survey, Persson (1977a,b) concluded a combined agonism and antagonism of LSD on dopamine receptors. This approach led Christoph *et al.* (1978) to suppose that dopamine receptors are able to go through a conformational change, depending on the availability of agonistic or antagonistic stimulation. Thus, a given allocation of agonistic binding sites makes LSD act as an antagonist, while normally it acts as an agonist (Kehr & Speckenbach, 1978).

On the D_2 receptor, LSD seems to act partially agonistically (Marona-Lewicka *et al.*, 2005; Minuzzi *et al.*, 2005). It seems to have a lower effect on the receptor than typical D_2-agonists, yet it is able to antagonize their effects (Walters *et al.*, 1979; White, 1986).

Watts *et al.* (1995) analysed binding and functional properties of LSD and other lysergic amides (cf. Figure 2.10) on dopaminergic D_1- and D_2-receptors in rats. All analysed substances acted competitively as agonists, both on D_1-receptors ([^{3}H]-SCH23390) and on D_2-receptors ([^{3}H]-spiperone plus non-flagged ketanserine) in the striata of rats.

Vollenweider *et al.* (1999) observed a significant increase in the binding of the D_2-antagonist [^{11}C]-raclopride in PET after administrating test persons with the LSD-related psilocybin.

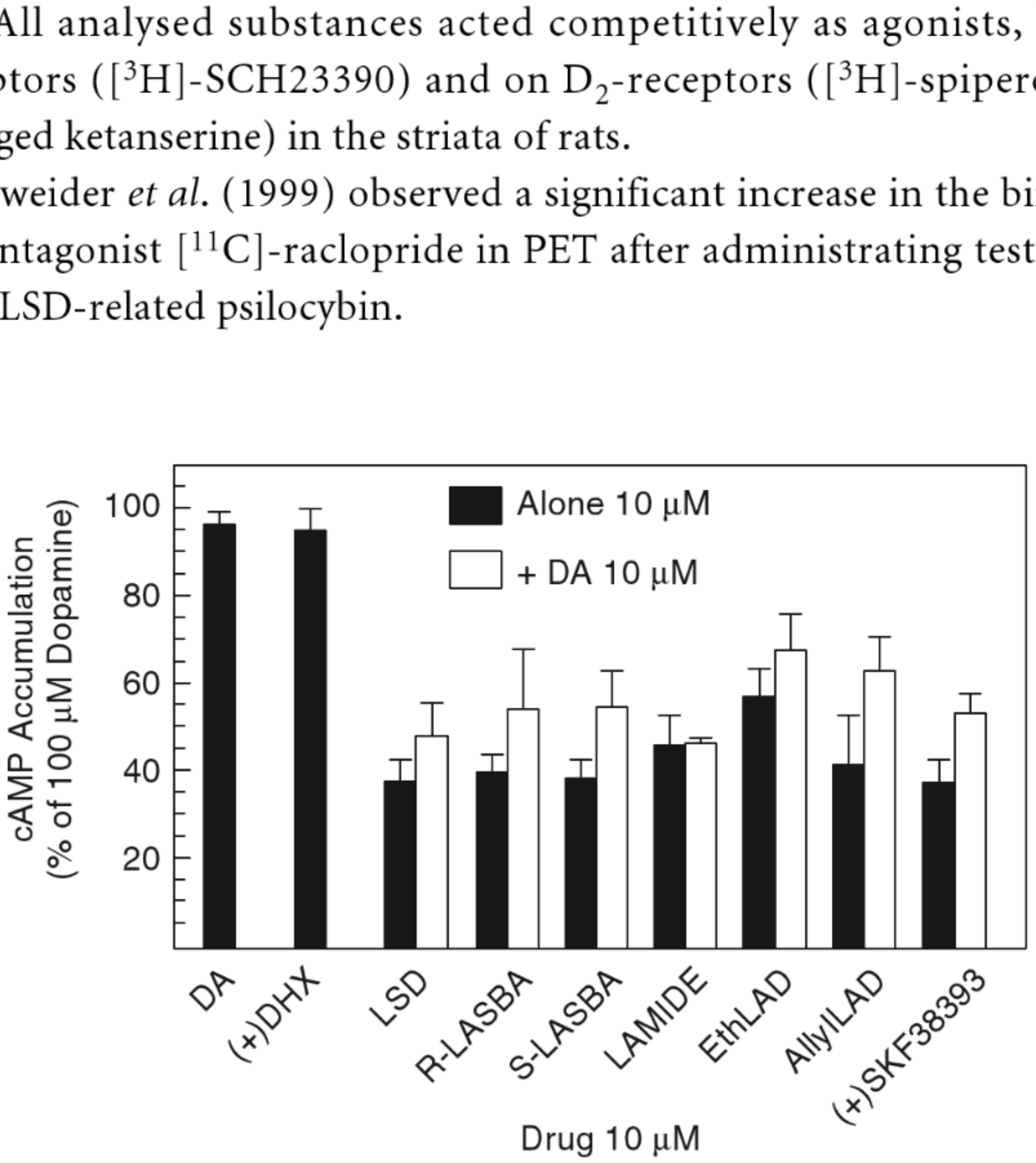

Fig. 2.10 LSD and related lysergic amides are partial agonists at D_1 receptors in rats. The ability of lysergic amide analogues to stimulate and block dopamine-mediated adenylate cyclase activity was measured in C-6 mD_{1A} cell membranes. The high-efficacy agonist (+)-DHX and the partial agonist (+)-SKF38393 were included for comparison purpose (Watts *et al.*, 1995, p. 406).

Thus, LSD stimulates the dopaminergic system. Interestingly, in contrast to many other dopamine-activating substances, it does not show any relevant dependence potential (e.g. Hoffmeister, 1975; Wiese, 1998; O'Brien, 2001). The cause could lie in the lack of dopaminergic activation of the nucleus accumbens, which, compared with cortical brain regions, does not exhibit elevated dopamine concentrations after administration of hallucinogenic substances (Erdtmann-Vourliotis *et al.*, 1999; Gresch *et al.*, 2002). The nucleus accumbens (a part of the striatum) is a central component of the 'reward system' in the brain (Trepel, 1999).

Potentiated effects by interaction at different receptors?

The affinity of LSD for 5-HT_{2A}- and 5-HT_{2C}-receptors does not differ significantly from that of phenethylamines (e.g. DOB and DOI). The hydrophobicity of LSD, DOB, and DOI is also comparable (Nichols *et al.*, 1977). Nevertheless, the *in vivo* potency of LSD is much higher than that of any other phenethylamine. There are reasons to believe that other pharmacologic properties are responsible for a possible potentiation of LSD effects. It is not easy to determine the responsible effect, however, since LSD binds with high affinity to a whole series of receptors such as 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_{5A}, 5-HT_6, and 5-HT_7-receptors, dopamine D_1 and D_2 receptors, and α_1-, α_2-, and β-adreno-receptors (Creese *et al.*, 1975; Burt *et al.*, 1976; U'prichard *et al.*, 1977; Dolphin *et al.*, 1978; Meibach *et al.*, 1980; Leysen, 1985; Hoyer, 1988; Lewicka & Nichols, 1995; Watts *et al.*, 1995; Nichols *et al.*, 2002; Glennon, 2003). Hallucinogenic phenethylamines show almost no affinity to these receptor types (Leysen *et al.*, 1989). It is unlikely that the effects occurring at the 5-HT_{1A} receptor are responsible for the enormous potency of LSD, since other indole systems such as psilocin and DMT show similar affinities for 5-$HT_{2A/2C}$ and 5-HT_{1A} receptors, while showing a considerably weaker effect.

LSD can also bind to α_2 adrenergic receptors with moderate affinity (Marona-Lewicka & Nichols, 1995). This could cause a potentiation of LSD effects. Dolphin *et al.* (1978) observed an interaction of LSD with central β-adrenergic receptors, both in the cerebral cortex and in C6-glioma cell cultures of rats.

The most probable causality for a synergistic potentiation results from interactions of LSD with the dopaminergic system. Though hallucinogenic tryptamines and penethylamines normally do not show an affinity for dopamine receptors, LSD has a high affinity for D_1 and D_2 receptors (Watts *et al.*, 1995). Besides, the affinity of LSD at the D_2 receptor ($K_{0,5}$ = 6.4 nM) is in a range in which a receptor activation takes place at clinically relevant doses.

The D_1 affinity is somewhat lower ($K_{0,5}$ = 27 nM), but yet remains relevant at a plasma concentration of 10–20 nM (Aghajanian & Bing, 1964).

Diab *et al*. (1971) used autoradiography on rats to show the bonding of [^{3}H]-LSD in numerous regions of the brain. Studies showed the highest binding density in the nucleus caudatus and in the nucleus accumbens of rat brains (McKenna & Saavedra, 1987). The regions where [^{125}I]-2-iodine-LSD and [^{125}I]-DOI bind to receptors in rat brains partially overlap, but in other regions the binding profiles vary strongly (McKenna *et al*., 1989). A number of analyses confirmed the dopaminergic effects of LSD (e.g. Von Hungen *et al*., 1974; Creese *et al*., 1975; Nichols, 1976; Ahn & Makman, 1979).

Marona-Lewicka and Nichols (2007) discovered that the course of effect was time dependent in discrimination studies with rats. If LSD is applied before testing, discrimination is induced by the activation of 5-HT_{2A} receptors. If the pre-treatment with LSD is undertaken 90 min prior to testing, D_2 receptors are activated. Substances activating the 5-HT_{2A} receptors then do not act as substituents any more. Dopamine agonists such as apomorphine can eliminate LSD after that duration of time.

All these data provide indications of a complex interaction between dopamine D_2- and serotonin 5-HT_{2A} receptors (Table 2.8). However, more analyses are necessary to clarify whether this accounts for the enormous effectiveness of LSD.

Synopsis of actions of LSD on receptors

The complex receptor interactions of LSD are a significant topic of experimental work and speculation about LSD's working mechanisms. The predominant hypothesis on how indole hallucinogens affect serotonin (5-HT) is summarized as follows: LSD acts to preferentially inhibit serotonergic cell-firing while sparing post-synaptic serotonergic receptors from up-regulation/down-regulation. This preference is shared in a somewhat limited fashion by non-indole hallucinogens. Non-hallucinogenic analogues of LSD show no such preference.

Serotonin (5-hydroxytryptamine; 5-HT) is produced by a small number of neurons (1,000s) that each innervate as many as 500,000 other neurons. For the most part, these neurons originate in the raphe nuclei (RN) of the midbrain. One major target of these is the locus coeruleus (LC), which controls the release of norephinephrine, which regulates the sympathetic nervous system. The LC also has neurons that extend into the cerebellum, thalamus, hypothalamus, cerebral cortex, and hippocampus. The RN extends its projections into the brainstem and up into the brain. It has been suggested that neurons in this brain region may inhibit sensation, thus protecting the brain from sensory overload. The fact that the LC and the RN innervate virtually

Table 2.8 Affinity of LSD to different receptors and receptor subtypes

receptor	Ki (nM)	species	origin	reference
5-HT_{1A}	1.1	Human	Cloned	
5-HT_{1B}	3.9	Rat	Cloned	Nichols *et al*., 2002
5-HT1C		Pig	Brain	Pazos *et al*., 1985b
5-HT_{1D}	14	Human	Cortex	Peroutka *et al*., 1989
5-HT_{1E}	93	Rat	Cloned	Nichols *et al*., 2002
5-HT_{2A}	2.7	Human	Cloned	Egan *et al*., 2000
5-HT_{2B}	30	Rat	Cloned	Nichols *et al*., 2002
5-HT_{2C}	5.5	Rat	Cloned	Nichols *et al*., 2002
5-HT_3	33000	Rat	Cortex	Milburn and Peroutka, 1989
5-HT_{4L}	1000	Rat	Cloned	Gerald *et al*., 1995
5-HT_{5A}	9	Rat	Cloned	Nichols *et al*., 2002
5-HT_{5B}	3.23	Rat	Cloned	Boess and Martin, 1994
5-HT_6	2.3	Human	Cloned	Hirst *et al*., 2003
5-HT_7	6.6	Rat	Cloned	Nichols *et al*., 2002
5-HT_{7L}	10	Rat	Cloned	Eglen *et al*., 1997
Adrenerg alpha	220	Rat	Brain	Prichard *et al*., 1977
Adrenerg $beta_1$	140	Rat	Cloned	Nichols *et al*., 2002
Adrenerg $beta_2$	740	Rat	Cloned	Nichols *et al*., 2002
Dopamine D_1	180	Rat	Cloned	Nichols *et al*., 2002
Dopamine D_2	120	Rat	Cloned	Nichols *et al*., 2002
Dopamine D_3	27	Rat	Cloned	Nichols *et al*., 2002
Dopamine D_4	56	Rat	Cloned	Nichols *et al*., 2002
Dopamine D_5	340	Rat	Cloned	Nichols *et al*., 2002
Histamine H_1	1540	Rat	Brain	Nichols *et al*., 2002

every part of the brain shows that serotonin can activate large portions of the brain from a relatively small area of origination (Hüther & Rüther, 2000).

In general, 5-HT may be seen as a mainly inhibitory transmitter; thus, when its activity is decreased, the next neuron in the chain is freed from inhibition and becomes more active. This view is limited by the fact that a few 5-HT receptors are excitatory ion channels (5-HT_3) and some subtypes may have excitatory effects, depending upon the G protein coupling within specific neurons. Since serotonergic systems appear to be intimately involved in the control of sensation, sleep, attention, and mood, it may be possible to explain

the actions of LSD and other hallucinogens by their disinhibition of these critical systems (Hüther & Rüther, 2000).

LSD acts as a 5-HT autoreceptor agonist on 5-HT_{1A} receptors in the LC, the RN, and the cortex. It inhibits firing and serotonin release of these cells. It also acts as a partial agonist on the post-synaptic 5-HT_{1A} site. LSD has high affinity for other 5-HT_1 subtypes 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1E}. Effects of LSD on 5-HT_{2C}, 5-HT_{5A}, 5-HT_6, and 5-HT_7 receptors (e.g. Erlander *et al.*, 1993; Lovenberg *et al.*, 1993; Monsma *et al.*, 1993) are described, but their significance remains uncertain. However, the hallucinogenic effect of LSD has been linked to its affinity for the 5-HT_2 receptor, where it acts as a 5-HT_2 agonist, as this property is shared by hallucinogens of the phenethylamine group (mescaline, 2,5-dimethoxy-4-iodoamphetamine, etc.) and the indoleamine group (psilocybin, DMT). A strong correlation was described between psychoactive doses of these hallucinogens and their respective potency at the 5-HT_2 receptor (Glennon *et al.*, 1988; Titeler *et al.*, 1988). Most data indicate a specific 5-HT_{2A} mechanism, although a 5-HT_{2C} effect cannot be ruled out.

LSD is probably best called a mixed 5-HT_2/5-HT_1 receptor partial agonist. Today it is believed that LSD is a partial agonist at 5-HT_{2A} receptors (e.g. Sanders-Bush *et al.*, 1988; Pierce & Peroutka, 1989), especially those expressed on neocortical pyramidal cells. Activation of 5-HT_{2A} also leads to increased cortical glutamate levels (Martin-Ruiz *et al.*, 2001; Winter *et al.*, 2004) probably mediated by thalamic afferents (Nichols, 2004). However, this increase in glutamate release can lead to an alteration in corticocortical and corticosubcortical transmission. LSD´s dual effect on 5-HT_2 (stimulatory) and 5-HT_1 (inhibitory) can explain how it may appear as an antagonist because it can modulate its own effect.

In a recent study, Gonzalez-Maeso *et al.* (2007) compared 2-HT_{2A} agonists with and without hallucinogenic activity in mice. It was found that these types of agonists differ with regard to the G-protein activation induced, especially those of the pertussis toxin-sensitive heterotrimeric $G_{i/o}$ and $G_{a/11}$ proteins and their coactivation. Using mice modified to genetically express 5-HT_{2A} receptors only in the cortex, it was shown that these receptors were sufficient to produce hallucinogenic effects (as indicated by hallucinogen-specific head twitch response) with identical firing rates of pyramidal neurons as without this manipulation. This may imply that the hallucinogenic effects are mainly mediated by cortico-cortical neural circuits, rather than by thalamocortical circuits, as proposed earlier by some scientists (Vollenweider & Geyer, 2001).

There is also evidence that LSD interacts with dopaminergic systems. In comparison with other hallucinogens, LSD interacts agonistically and antagonistically with central dopamine D_1 and D_2 receptors (von Hungen *et al.*, 1974;

Watts *et al*., 1995). It is not established how these changes are involved in the psychoactive effects of LSD, but studies with related, but more selective 5-HT_{2A} hallucinogen psilocybin demonstrated an increased release of dopamine, as evidenced by a 20% decrease of [^{11}C]raclopride binding after psilocybin in human subjects (Vollenweider *et al*., 1999).

Marona-Lewicka *et al*. (2007) discovered receptor activation by LSD to be time dependent. LSD in rats 15–30 min prior to testing in a discriminative stimulus task leads to 5-HT_{2A} activation, while after 90 min D_2 receptors may mediate major parts of LSD reactions. These data suggest an interaction between dopamine and serotonin receptors and might be a possible explanation for the enormous range of effects LSD engenders in humans.

Pharmacological and toxicological effects

Already, shortly after the discovery of LSD, numerous scientists had started looking into its numerous effects. For example, changes in heart frequency, blood pressure, respiration, skin temperature, and pupil size were specified on numerous occasions, with partly contradictory results (Busch & Johnson, 1950; Forrer & Goldner, 1951; Savage, 1952). Besides a seemingly large variance between the effects, the discrepancies could be caused by the almost incommensurable test conditions. Some examiners chose test persons who were ill and others chose healthy ones for their studies. In addition, different doses and styles of application were used and the time periods between intake, onset of effects, and measuring points were often not sufficiently specified. Moreover, the setting variables were apparently not sufficiently considered, so the contradictory results could partly be ascribed to (secondary) psychic reactions and their somatic effects.

Acute effects and toxicity

LSD's LD_{50} varies from animal species to species, whereby rabbits are the most sensitive (0.3 mg/kg; Cerletti & Rothlin, 1957). Doses of 16.5 mg/kg led to the death of rats from respiratory failure and cramp (Cerletti & Rothlin, 1957; Freedman, 1969). Mice tolerated doses of 46–60 mg/kg i.v. (Rothlin, 1956; Cerletti & Rothlin, 1957). In a single experiment, an elephant died after receiving a dose of 297 mg LSD (West *et al*., 1963). The lower oral threshold where humans show measurable sympathomimetic effects is about 0.5–1.0 μg/kg. There are no verified cases of death by means of an LSD overdose (Cohen, 1967; Hofmann, 2002).

Based on hypothetical interpolation, the LD_{50} in humans (adult, male) was in fact assumed to be 14 mg (Hoffer, 1965), but much higher doses were survived (Wock *et al*., 1974).

There is no other known ergot alkaloid that induces such distinctive effects in such small doses. The effects of LSD take on many forms and variations (Figure 2.11). Besides ataxy, paralyses, and temporarily enhanced reflexes, numerous vegetative symptoms are observable. Even after the comprehensive observations by Grof (1983) on hundreds of individuals in thousands of LSD sessions, there is no one symptom that can be observed with absolute regularity. Respiratory disturbances with paroxysmal apnoea already occur in animals after (very high) doses of 50–100 μg/kg and seem to be an expression of direct LSD effects on the respiratory centre of the medulla oblongata (Rothlin, 1956).

In some experiments, rats were administered LSD (2.5 mg/kg i.v.) for 30 days, whereby all animals survived. Since the maximal tolerated single dose of LSD is 3.2 mg/kg, no cumulative factors seem to play a role in the excretion of LSD. Rats develop symptoms such as tremor, enhanced reflexes, and pilo-erection when chronically administered with LSD, although these relatively unspecific signs lose their intensity within a few days (Rothlin, 1956).

Cardiovascular effects

LSD influences the cardiovascular system due to its sympathomimetic effective components and anxiety induction. The consequences are an increase in

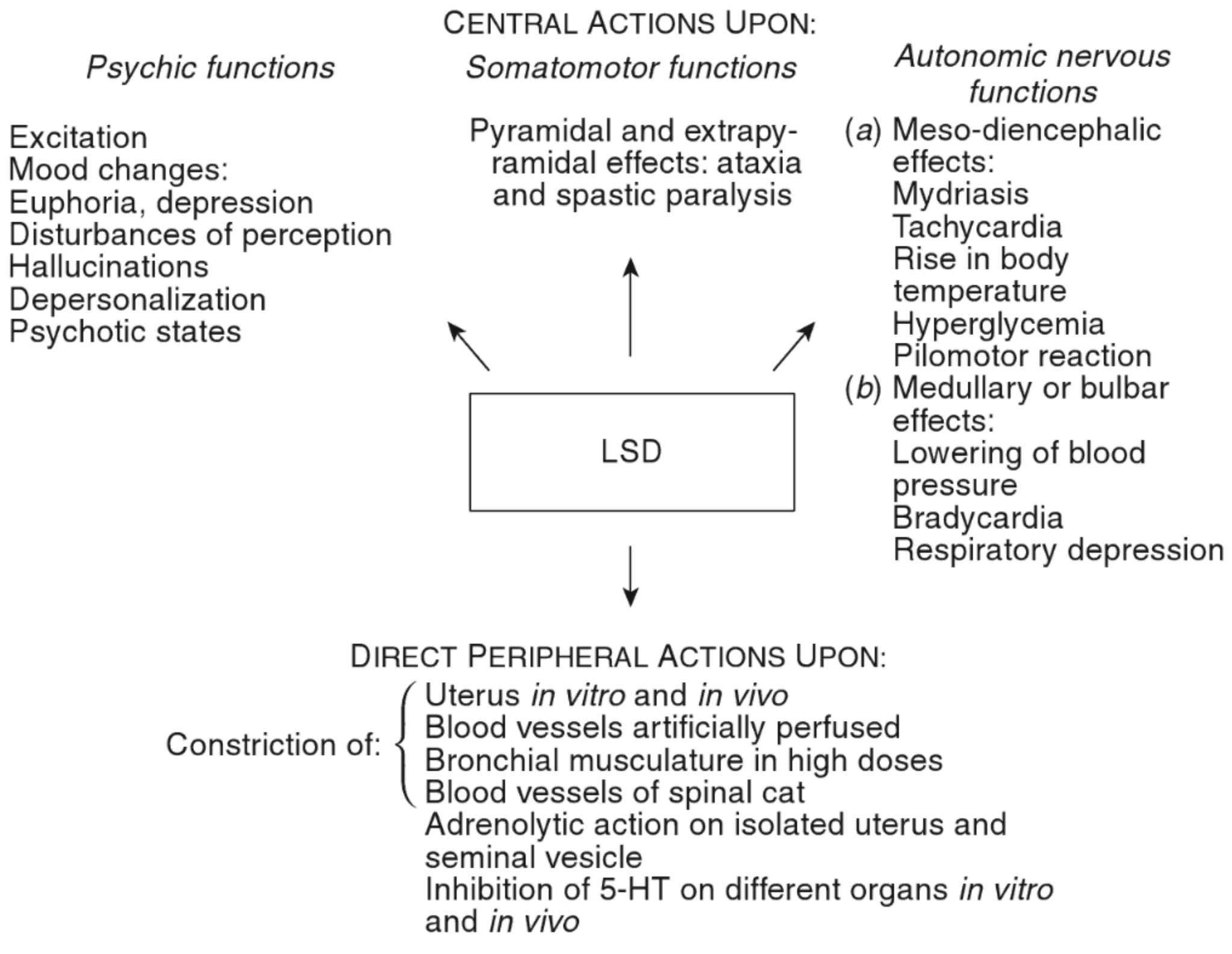

Fig. 2.11 Summary of general pharmacology of LSD (Rothlin, 1957b, p. 669). Please note: virtually all physiological changes are only mild to very mild and have great interindividual variability.

blood pressure, mainly systolic, and heart frequency (e.g. Rothlin, 1956; Hertle *et al.*, 1962).

After LSD administration (double-blind, cross-over, $n = 6$, 1 µg/kg, p.o.) there was an increase in heart frequency of 11% after 1.5 h, after a further 3 h even of 18% (DiMascio *et al.*, 1957a). Forrer and Goldner (1951), by contrast, described a dose-dependent increase in heart frequency for 1–2 h at the most. The pulse frequency during control days was more stable than during the interview. After LSD administration (double-blind, crossover, $n = 1$, 1 µg/kg, p.o.) the frequency behaved the other way around; here, bigger oscillations were observed during the stationary phase (Table 2.9). In general, the heart frequency was raised during the entire measuring phase (DiMascio *et al.*, 1957b). Hertle *et al.* (1962) confirmed these results (open, $n = 7$, 1 µg/kg, i.v.).

The systolic blood pressure in experiments by DiMascio *et al.* (1957a,b), as well as by Forrer and Goldner (1951) displayed an increase of 12% after 2.5 h, slowly normalizing afterwards, whereas by contrast the control persons displayed oscillations of 2.8% at most. The diastolic blood pressure in this series of tests was raised by 10%; control data exhibited oscillations of only 1.5%. Hertle *et al.* (1962) mainly observed increases as well as decreases in blood pressure, with a tendency to larger amplitudes after LSD administration (open, $n = 7$, 1 µg/kg, i.v.) (Table 2.10).

Table 2.9 Effects on pulse, respiration, and body temperature before (I); and 180 min after (II) 120 µg LSD i.v. (Sokoloff *et al.*, 1957)

Subjects	Age	Sex	Pulse/min		Respiration/min		Temperature in °C	
			I	II	I	II	I	II
13	18–46 ø 24	w = 5 m = 8	78	91	17	18	36.9	36.9

Table 2.10 Blood pressure and heart rate changes during acute effects of moderate doses of LSD. (SD = standard deviation)

Parameter	Sokoloff *et al.*, 1957 (n=13, 120 µg i.v.)	DiMascio *et al.*, 1957a (n=6, 1µg/kg p.o.)	Kornetsky 1957 (n=10, 100 µg p.o.)
Arterial blood pressure (mm Hg)	+5 SD 2.9	+12% (syst.) +10% (diast.)	+13 (SD unknown)
Heart rate (beats per min)	+15 SD 7	+18%	+19 (SD unknown)

ECG revulsions in humans (open, $n = 7$, 1 μg/kg, i.v.) yielded rather uncharacteristic changes. Only ST minimal segment depressions and marginal T wave flattening were found (Hertle *et al.*, 1962).

On the quest to find pathological changes of the heart, neither macroscopic nor microscopic changes could be detected in rabbits (5 mg, i.v.) or mice (0.03 mg, i.p.), respectively. Even the tests of liver and kidneys of these animals post mortem did not yield any injuries (Hassler, 1964).

Respiration

The breathing rate after LSD administration in humans (1 μg/kg) was increased by 8% (DiMascio *et al.*, 1957a). Forrer and Goldner (1951), by contrast, could not find consistent tendencies concerning the changes in breathing frequency. In another study, the inspiration/respiration ratio raised continuously during the entire measuring period (7.5 h); maximizing at 16% at the end (DiMascio *et al.*, 1957a).

Bhattacharya (1955) found a stimulating effect of LSD on guinea pig's bronchial muscle tissue in vitro.

Body temperature

Delphaut and Lanza (1960) reported an increase in body temperature of 1–3°C in rats given LSD. Other authors have confirmed these results in rabbit studies (e.g. Supek & Milkovic, 1955; Eichenberger & Friolet, 1957; Jacob *et al.*, 1964). Rothlin (1956) showed a dose-dependent increase in rectal temperature in rabbits starting at only 0.5 μg/kg i.v. LSD. Calorimetric measurements showed that LSD primarily impairs the release of heat. In studies on dogs, Bircher *et al.* (1958) showed a temperature increase of 1.4°F after intraventricular injection

Table 2.11 Measurements of somatic parameters during acute effects of a medium dose of LSD (n=13, 120 μg LSD i.v.) from Sokoloff *et al.* 1957. (N.S. = not significant compared to controls.)

Physiological parameters	Changes during LSD
Respiration rate per min.	N.S.
Oral temperature	N.S.
Blood oxygen saturation (%)	N.S.
Blood CO_2 tension (mm Hg)	N.S.
Blood pH	N.S.
Blood glucose concentration in mgs. %	N.S.
Hemoconcentration	+ 0.57 gr. % SD 0.34

of 100 μg LSD. After i.v. administration of 100 μg/kg, body temperature increased by 2.1°F. Interestingly, in pigeons, LSD causes the body temperature to drop (Hoffman, 1958).

Neuhold *et al.* (1957) tried to identify the site of pyretogenic and motor-stimulating effects of LSD by successively removing parts of the brain. In decorticated rabbits, LSD-induced hypothermia (5 μg/kg, i.v.) occurs as usual without any change. In decorticated mice and rabbits, the increase in spontaneous motility due to LSD is also the same as in normal animals. Yet such effects of LSD are absent after removal of the diencephalon or cerebrum. Thus, the pyretogenic and motor effects of LSD may be assumed to target a subcortical and quite likely diencephalic area of the brain.

After giving animals (e.g. rabbits, cats, and dogs) LSD (0.5–50 μg/kg, i.v. or s.c.), Horita and Dille (1955) reported an increase in rectally measured body temperature. The maximum increase occurs after about 1 h and lasts up to 8 h. After removal of the cervical spinal cord in rabbits, the pyrogenic effect of LSD disappears.

An increase in body temperature after LSD administration has also been observed in humans (open, controlled, $n = 6$, 1 μg/kg, oral dose; Forrer & Goldner, 1951). The skin temperature in humans has been shown to decrease slightly (DiMascio *et al.*, 1957a) after administration of LSD (1 μg/kg). There are two anecdotal reports about hyperthermia from LSD ingestion (Friedman & Hirsch, 1971a, Lishow 1971).

Eyes

There is a reliable and dose-dependent dilation of the pupils after taking LSD. However, according to Grof (1983), who has conducted extensive observations, exceptions are not uncommon. A rapid dilation of 53% after LSD (1 μg/kg), which after 7.5 h was still 24%, is only one of many findings (DiMascio *et al.*, 1957a) (Figure 2.12). Chessick *et al.* (1964) reported that dilation was greater after a dose of 1.5 μg/kg, than after 1 μg/kg LSD, yet comparable to that observed after a dose of 3 μg/kg. At this level, tolerance was shown to develop after 6 days. Other authors have reported that pupil size is directly proportional to dosage level (0.5–6.0 μg/kg, oral dose) and that at high doses there is even a reduced response to light (Forrer & Goldner, 1951).

A photographic study was conducted on 20 men to show the difference in pupil size before and after LSD administration. Two hours after being given LSD (controlled, 75 μg, oral dose) there was an average increase in pupil size of 1.2 mm (after placebo: 0.16 mm) (Freeman, 1958).

Payne (1965) studied the rate of change in accommodative convergence divided by associated change in accommodation (AC/C ratio) for the purpose

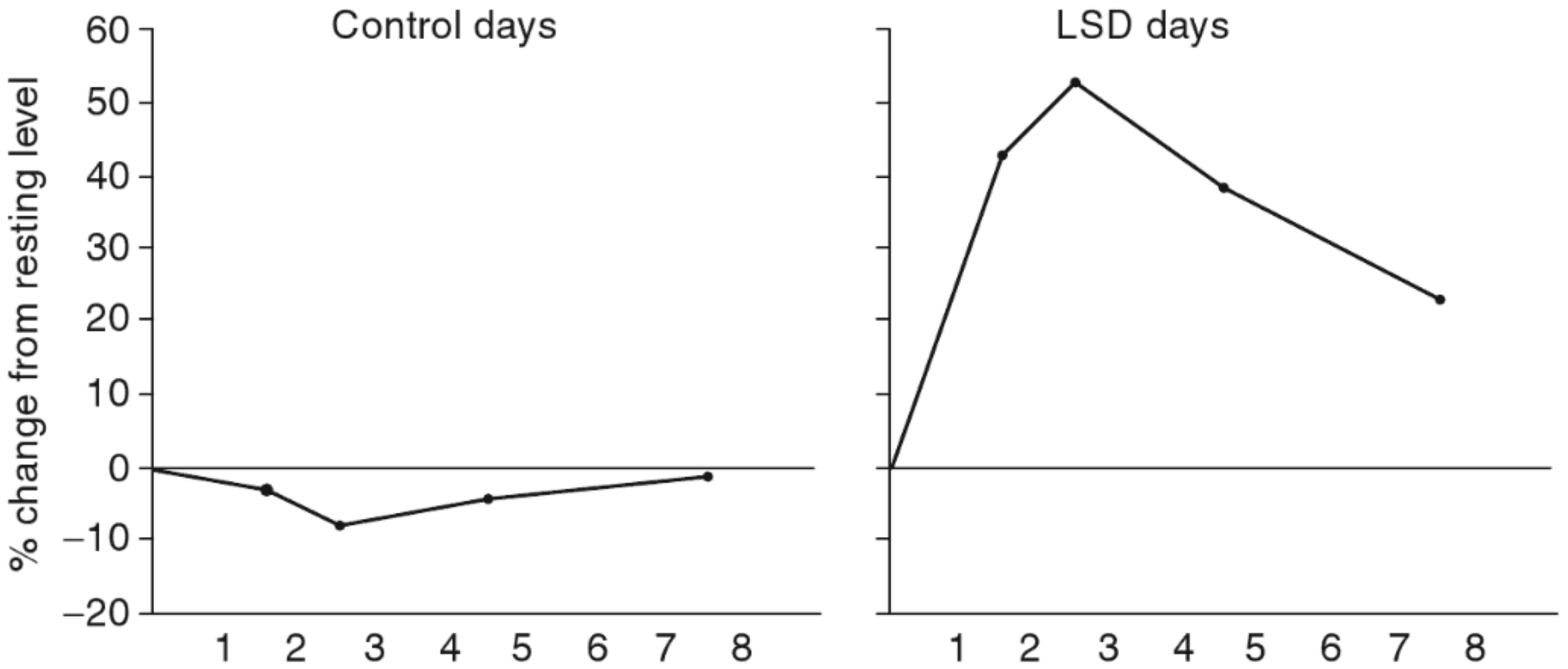

Fig. 2.12 Pupil size after 1 μg/kg LSD p.o. for 7 days (from DiMascio *et al.*, 1957a, p. 313).

of precisely estimating accommodation over the entire radius of action in healthy subjects who were given LSD (double blind, crossover, $n = 10$, 0.7–2.8 μg/kg, oral dose). LSD produced a slight, but definite increase in the AC/C ratio, which, according to the author, was produced by partial transient paralysis of the ciliary muscle (cycloplegia). There was no correlation between individual changes in AC/C ratio, LSD dosage, and amount of pupil dilatation.

Holliday and Sigurdson (1965) tested the influence of LSD (double blind, crossover, $n = 11$, 1 μg/kg, oral dose) on intraocular pressure (IOP) in healthy individuals. There was a significant increase in IOP 1.5 h after taking LSD. Changes were accompanied by marked changes in systolic and diastolic blood pressure, although the latter could also be related to anxiety-producing test conditions and thus autonomic nervous system effects. The increase in IOP was not clinically relevant at this dosage level. The authors suggest, however, that higher doses, which are already in common use, would produce much higher values. There are at present no data on acute glaucoma after taking LSD.

Lacrimation may also increase, depending on dosage level. Direct injection of 1 μg LSD into the eye has been shown to lead to only slight dilation (Forrer & Goldner, 1951).

Gastrointestinal tract

In a study on 12 subjects who were given 60–100 μg LSD, Quick's hippuric acid test (with or without benzoic acid loading) was performed and showed no change. However, the much more sensitive Snapper–Saltzman test revealed minimally abnormal liver function. While the extreme sensitivity of the Snapper–Saltzman test may make it prone to false results, the authors do not rule out the possibility of impaired liver function (Fischer *et al.*, 1951a). In a

study by Belsanti (1952), the Snapper–Saltzman test showed that LSD (open, crossover, $n = 14$, 80–480 μg, oral dose) led to increased excretion of glucuronic acid, which the author suggested may represent a latent change in the liver.

These findings have been disputed by other authors. Some cite stable 'non-protein nitrogen' levels (nitrogen present in blood and tissue which is not contained in proteins) and the 'cephalin-cholesterol flocculation test' (Forrer & Goldner, 1951) as evidence of normal liver function.

LSD (1 mg/kg, intraperitoneal) causes a rapid and marked (completely reversible after 24 h) change in free electrophoretic protein patterns in the liver (Missere *et al*., 1961).

Endocrine function and body weight

To study the metabolic effects of LSD, Sackler *et al*. (1966) gave high doses of LSD (500 or 750 μg/kg, s.c.) to female rats every other day for 14 days and then measured their body weight. No significant change was seen, although the 750 μg/kg group decreased food intake markedly.

At the end of the study, the endocrine organs were weighed. There was a notable decrease in thymus tissue. The relative weight of the adrenal glands increased, while the weight of the uterus and thyroid gland decreased. In a study on male rats, Weltman and Sackler (1966) reported a significant reduction in food intake, oxygen consumption, and metabolic rate. There was a clear dose-dependent reduction in body weight. There was also a significant decrease in the weight of the spleen, thyroid gland, and seminal vesicle. Unlike in the female rats, there was a significant increase in absolute weight of the adrenal glands. Given that there was a reduction in total leucocytes, lymphocytes, and eosinophils, the diminished weight of the thymus may be explained by an increase in adrenocorticosteroid output, since these cells and organs are parameters of adrenocortical function. The increased weight of the adrenal glands would further support this explanation. Indications of diminished thyroid function due to chronic LSD use are seen in a reduced desire to eat, lower glandular weight, and reduced oxygen intake. To summarize, it may be said that long-term administration of very high doses of LSD in animals stimulates adrenal gland function, lowers metabolism, and inhibits thyroid, and probably gonadal function. After the fifth injection, the 17-ketosteroid values in 24-h urine were measured. The 750 μg/kg group exhibited a significant rise in steroid levels of around 39.7% over controls. The other test group had an average increase of 25.1%.

Collu *et al*. (1975) gave male, prepubescent rats very high doses of LSD (100 [A] or 500 [B] μg/kg, intraperitoneal) 3 times weekly for 1 month. Food intake decreased slightly only in group B, although body weight decreased

significantly in both groups. In group B, there was a significant decrease in plasma levels of growth hormone (GH), and in group A, of the GH content of the hypophysis decreased. Plasma levels of luteinizing hormone (LH) were not modified by LSD. However, in group A, the LH content of the hypophysis was much lower. Plasma and hypophyseal levels of follicle-stimulating hormone (FSH) remained unchanged in both groups.

In a study by Rinkel *et al*. (1955), excretion of 17-ketosteroid after administration of ACTH and LSD (open, controlled, $n = 15$, 0.5 µg/kg, oral dose) was significantly increased.

Meltzer *et al*. (1981) gave human test subjects LSD (open, $n = 3$, 100 µg, oral dose) and reported increased serum STH, but unchanged prolactin levels.

Kidneys

Hollister (1968b) suggested that LSD exerts direct glomerular and tubular effects, citing studies that showed reduced excretion of urea and 17-ketosteroiden after LSD administration (500 µg, intraperitoneal) in rats (Siva Sankar, 1960; Siva Sankar *et al*., 1962b) and signs of a diminished glomerular filtration rate in humans.

In a dog study, Barac (1957) showed that LSD has an antidiuretic effect (100–300 µg/kg). Kies *et al*. (1957) conducted three experiments with seven men who were given LSD. In well-hydrated test subjects, after i.v. injection of 100 µg LSD (about 1.5 h post-injection, duration: 1 h), a marked antidiuretic effect and increased levels of chloride in urine were observed. Afterwards, diuresis was observed. The authors suggested that an antidiuretic effect might have been caused by hypothalamic stimulation.

In a study by Hollister *et al*. (1970), subjects exhibited initial antidiuretic effects of LSD (open, crossover, $n = 14$, 1.5–2.0 µg/kg, oral dose) already after half an hour. Some had complete suppression of urine production for at least half an hour. It took more than 4 h before uresis normalized. Compared with control days, the excreted amount of urine on the test day was greater at the beginning and much lower after 1 h. Even 4 h after taking LSD, the amount of excreted urine remained much lower. On the test day, urine osmolality was low, but rose as more water was retained. Measurements of Na^+- and Cl^- values did not reveal any uniform tendencies. It should be noted when interpreting these results that secondarily increased stimulation due to LSD events can also alter the overall psychophysical balance and thus lead to changes in uresis.

Siva Sankar *et al*. (1962b) reported reduced excretion of ketone bodies in a study with 16 rats that were given LSD (500 µg, intraperitoneal).

Neurophysiological effects

LSD, especially in high doses, is known to produce certain measurable and sometimes obvious neurological changes (Logan, 1975).

Studies have shown profound activation of the autonomic nervous system after intracerebral LSD injection in dogs (20–140 μg) and cats (34–210 μg). Reported symptoms include increased salivary flow, spontaneous vomiting, micturition, and mydriasis (with reactive pupils). Increased perspiration and hypersensitivity to light, noise, and touch were only seen in cats. Ataxia has been observed in dogs (Haley & Dasgupta, 1958).

A study on eight monkeys who were given LSD (1 mg/kg, i.v.) reported an absence of pain reflexes (up to 65 min post-injection) and lacking response to visual stimuli. Pupillary reflexes to light were present throughout the entire test period, although there was marked ataxia for about 1 h. Muscle strength, deep tendon reflexes, vestibulo-ocular movements, and reactions to auditory stimuli were not greatly altered (Evarts, 1956). In a study by Forrer and Goldner (1951), subjects who were given LSD (0.5–6.0 μg/kg, oral dose) exhibited dose-dependent hyper-reflexia and mild signs of an uncertain gait, but no coordination problems or nystagmus.

One of the most noticeable neurological effects associated with LSD is change in pupil size induced by its sympathicomimetic effects.

In cat studies, high doses of LSD (100–200 μg, intraventricular administration) have been shown to reduce or suppress the pressor reflex, with a drop in blood pressure of 10–20 mmHg. Yet, i.v. administration of LSD at the same or higher doses does not produce any such effect (Ginzel, 1955, 1956). In bilateral vagotomized cats, LSD (20 μg/kg, i.v.) has been shown to inhibit an increase in blood pressure due to bilateral carotid occlusion (Weidmann & Cerletti, 1958).

Studies in humans (e.g. Hertle *et al.*, 1962) and animals (e.g. Little *et al.*, 1957; Haley & Dasgupta 1958) have shown that LSD facilitates responses of monosynaptic reflexes.

The effect of 3 μg/kg LSD on the threshold of the patellar tendon reflex has been shown to be greater than that for 1.5 or 1.0 μg/kg LSD, with the latter not resulting in any significant difference (Chessick *et al.*, 1964).

Geiger and Cervone (1958) severed the lower cervical spinal cord in cats and stimulated peripheral nerves (0.08–3.0 volts) for 0.1–0.4 ms after administering LSD (4–1000 μg/kg, i.v.). Enhanced monosynaptic reflexes were observed at dosages above 200 μg/kg LSD. The increased amplitude of monosynaptic spikes was notable after 15 s and lasted up to 3 h. Maximum reflex facilitation occurred at 250–300 μg/kg LSD. Higher doses only prolonged the effects.

The inhibition of polysynaptic activity was accompanied by facilitation of monosynaptic reflexes.

Cerebral blood flow

The fact that serotonin is a vasoconstrictor and that LSD has a serotonin–antagonist effect on vessels led to the hypothesis that the hallucinogenic agent may possibly influence cerebral blood flow. Normal brain functioning is highly dependent on a continual supply of essential substances, particularly glucose and oxygen. Thus it was proposed that a potential relationship exists between energy delivery to the brain as a result of altered physiological and/or biochemical states and psychological effects.

The only study in this regard by Sokoloff *et al.* (1956, 1957) found that after administration of LSD (open, crossover, $n = 40$, 120 μg, i.v. administration) there was no significant change in cerebral blood flow, vascular resistance in the brain, glucose and oxygen consumption, arteriovenous oxygen and glucose difference, or respiratory quotient. Only a slight increase in average arterial blood pressure and moderately elevated arterial haemoglobin concentrations (related to increased oxygen levels in peripheral blood) were observed.

Electroencephalography (EEG)

Although several EEG studies have been conducted to examine the effects of hallucinogenic substances, the results have not greatly contributed to our understanding of their mechanism of action. In human studies, only scalp electrodes have been used, while in animal EEG studies, intracerebral measurements have been made at various dosages (Evarts, 1957; Fink, 1959; Were, 1964).

Most results from human EEG studies demonstrate only moderately altered brain activity. Gastaut *et al.* (1953) reported only slight deviations from normal brain activity in 7 of 12 test subjects (40–60 μg oral LSD). Alpha frequency increased by an average of around 1.75/second. According to studies by Rinkel *et al.* (1952) and Anderson and Rawnsley (1954, n = 23, 100 μg, oral dose), the only change on EEG is a slight increase in the frequency of the alpha rhythm (see also Bente *et al.*, 1957a,b; Apter & Pfeiffer, 1957). Sanguineti *et al.* (1955) reported a quantitative increase in the alpha rhythm 1–3 h after administering LSD ($n = 15$, 50–400 μg, oral, i.v. or i.m.), without any effect on variability of cerebral rhythm.

Other authors have found no significant changes on EEG readings after administration of LSD (Forrer & Goldner, 1951; Bradley *et al.*, 1953; Elkes *et al.*, 1954).

Bente and Itil (1957) reported that after administration of LSD (40–60 μg, i.v.) there was a marked acceleration in frequency, which was characteristically associated with marked rhythmization. Thus, slow diffuse dysrhythmias could be successively transformed into rhythmically stabilizing alpha frequencies. The effects of LSD were primarily characterized by a marked depression of spontaneous electrical brain activity accompanying this acceleration. This would manifest in increasing flat EEG phases, which at the height of the drug's effects become considerably more prolonged and later reappear intermittently altering with rhythmic, accelerated background activity.

EEG studies taken after administration of LSD show progressive desynchronization due to quantitative reduction of slow components of the resting EEG (Elkes *et al*., 1954; Werre, 1964; Rodin & Luby, 1966; Shagass, 1966; Itil, 1969).

Shirahashi (1960) reported that after administration of LSD (open, cross-over, $n = 6$, 50 μg, oral dose) changes on EEG readings were apparent only during visual phenomena. The onset of optical pseudohallucinations was associated with suppression of the alpha rhythm.

In a quantitative analysis of changes seen on EEG, Goldstein *et al*. (1963) and Pfeiffer *et al*. (1959, 1962) reported that healthy subjects had variable, but organized activity. After being given LSD, average energy output and variability were diminished. In chronic schizophrenics, energy output did not change after being given LSD, but variability increased to a maximum after 1.5 h. Goldstein *et al*. (1963) reported decreased variability of about 33% without significant changes in average energy level after administration of LSD (open, cross-over, $n = 30$, 0.3–1.0 μg/kg, oral dose). Increasing the dose to 1.0 μg/kg LSD led to a decrease in variability of 25%, and a 23% reduction in energy level.

The increased frequencies related to hallucinogenic substances resemble findings on the effects of other CNS stimulants. There are, for instance, similarities between the EEG effects of LSD and amphetamines. Both substances produce a significant reduction in voltage; yet the effects of LSD appear to be more gradual and longer lasting (Bente & Itil, 1957; Murphree *et al*., 1962) (Table 2.12).

There are only a few studies on electrical activity in deep brain structures. In one study, epileptic patients who were given LSD (open, cross-over, $n = 2$, 50–150 μg, oral administration) had marked levelling of spike and sharp-wave complexes. Existing paroxysmal activity was enhanced in three chronic schizophrenics (Sem-Jacobsen, 1956; Schwarz *et al*., 1956a).

Monroe *et al*. (1957) implanted subcortical and cortical electrodes in schizophrenic patients for electrostimulation. In hippocampal, amygdalar, and septal

Table 2.12 Summary of the effects of LSD on EEG (from Fink & Itil, 1968)

EEG	Effect of LSD
Alpha abundance	Decrease
Alpha mean frequency	Increase
Beta abundance	Increase
Theta abundance	No change (decrease)
Delta abundance	None (or decrease)
Amplitude	Decrease
Variability	Increase

regions, LSD was shown to induce (open, cross-over, $n = 6$, 50–200 μg, oral dose) subcortical paroxysmal activity, which was associated with manifestations of anxiety and pseudohallucinatory phenomena.

Based on these results, administration of LSD to humans at clinically relevant doses produces slightly desynchronized EEG patterns. Other psychoactive stimulants produce similarly non-specific effects. Hollister has suggested a relationship between the changes seen on EEG and pseudohallucinations. However, such symptoms typically appear without any modification of electrical activity in the brain (Hollister, 1968d).

There have been reports of epileptic seizures after taking LSD, although the incidence is very low and the significance questionable (Baker, 1964; Cohen, 1966; Fisher & Ungerleider, 1967; Smart & Bateman, 1967).

While it is possible that chronic LSD may be related to increased delta, theta, alpha, and beta EEG activity (Blacker *et al*., 1968), this has not been confirmed (Leuner, 1981; Grof, 1983).

Evoked potentials

Bachini *et al*. (1965) examined the effects of LSD (double-blind, cross-over, $n = 20$, 1–1.5 μg/kg, i.m.) on visual evoked potentials (VEPs) after continuous stimulation with a flickering light for 45–90 min in the dark. Complex changes were seen in VEPs, which the authors suggested indicated modifications in temporal ordering of visual information. The main effects of LSD were multiplication of VEP waves and increased amplitude. The authors suggest that these results support a disinhibiting effect of LSD on visual inflow. Prieto *et al*. (1965) also reported altered VEPs (increased amplitude, multiplications of waves) after LSD administration (open, crossover, $n = 34$, 0.1 mg, i.m.).

In a study by Rodin and Luby (1966), the 'rhythmic after-discharge' of the VEPs disappeared in most subjects after they were given LSD (open, cross-over, $n = 8$, 1 μg/kg, i.v.) and amplitude decreased.

Shagass (1966) reported significant changes in VEPs, which were mainly received from the left side of the head. In general, LSD (no description of study design, $n = 17$, max. 2.5 μg/kg, i.v.) led to reduced amplitude and increased frequency of visual evoked after-rhythms.

Bradley *et al.* (1953) reported (open, crossover, $n = 15$, 15–100 μg, oral dose) enhancement of LSD-induced effects after rhythmic light stimulation with a stroboscope. It is noteworthy that one-third of test subjects were in a trance-like state during light stimulation and three exhibited catatonic behaviour.

In a study by Brown (1968), LSD (open, crossover, $n = 17$, 0.75–1.0 μg/kg, oral dose) was given to nine 'visualizers' (people with the ability to generate vivid visual imagery) and eight 'non-visualizers'. All visualizers experienced enhanced sensory perception, while non-visualizers had only minimal changes in colour perception (without modification of depth, position, or proportion). The effects of LSD were also longer on average in the visualizers. EEG studies showed significant differences between the two groups in response to colour, especially green/blue and red. Diminished EEG activity was seen only in non-visualizers, who had already demonstrated in a control run greater activity, with significant differences in alpha-wave frequency and amplitude.

Carlson (1958) reported that healthy subjects who were given LSD (open, cross-over, $n = 9$, 50–100 μg, i.v.) initially had dark adaptation curves. LSD increased the absolute visual threshold of all curves, with a more pronounced effect on the photopic threshold. The variability of threshold values did not increase.

Ostfeld (1961) conducted various tests on healthy subjects who were given LSD (single blind, crossover, $n = 14$, 25–100 μg, oral dose). Only at higher doses (75 μg or more) were there changes in the pattern of dark adaptation curves. Large doses of LSD produced electroretinogram (ERG) readings which showed increased scotopic beta-wave amplitude (and often also of the alpha wave). During this time, test subjects reported pseudohallucinations. These results demonstrate significant modifications in retinal function associated with optical changes in perception.

Other studies have shown an apparently diminished intensity threshold for light (dark adaptation of the cones was inhibited while that of the rods was enhanced) and a lower threshold for flickering light on ERG. Yet the threshold of Critical Flicker Frequency in humans has been shown to increase after administration of 25–50 μg LSD (Takashina, 1960). Holliday *et al.* (1965) examined the effects of LSD (open, crossover, $n = 10$, 1 μg/kg, oral dose) on

Critical Flicker Frequency in healthy test subjects. After taking LSD, it was significantly reduced. The authors thus concluded that LSD reduces the excitability threshold in the retinocortical system.

Miltrani *et al*. (1972) tested the speed of saccadic eye movements in healthy individuals before and after administering LSD (open, crossover, $n = 5$, 100 μg, oral dose). There was no change in average or maximum speed after taking LSD.

Arnold *et al*. (1971) reported that LSD had no effect on auditory evoked potentials (AEPs) in study subjects ($n = 8$).

Shagass *et al*. (1962) examined electrically evoked potentials on the somatosensory cortex and response to various dosage levels of LSD (no description of study design, $n = 10$, 50–150 μg, i.v.). The changes observed in intensity–response function were inconsistent and not significant.

The effects of LSD in blind patients

Ostfeld (1961) examined reactions in completely blind subjects (i.e. no light perception and no measurable electrical retinal activity) to LSD (single blind, crossover, $n = 17$, 75 μg, oral dose). Nearly all subjects reported a marked increase in 'unusual visual experiences' after being given LSD. These seemed to resemble pseudohallucinations in people who can see, but were less frequent. Instead, blind patients experienced more auditory, tactile, gustatory, and olfactory pseudohallucinations. Thus, a functioning retina is not absolutely essential to experiencing optical pseudohallucinations.

Krill *et al*. (1963) also conducted LSD studies with completely blind subjects (double blind, crossover, $n = 24$, 1 μg/kg, oral dose). Thirteen study subjects reported visual pseudohallucinations after being given LSD. Based on their descriptions, these resembled those experienced by people who can see. All subjects who reported pseudohallucinations also reported prior spontaneous visual experiences. Patients without a history of pseudohallucinations did not have any under the influence of LSD. ERG was performed on two patients with total optic nerve atrophy, but intact retinas. Changes seen on ERG resembled those in people with normal vision who have optical pseudohallucinations (Krill *et al*., 1960).

Electrical stimulation of the eye

Knoll *et al*. (1963) conducted experiments to trigger phosphenes (i.e. appearance of light) using specific electrical stimuli. During stimulation with square pulses within an encephalographic frequency range (1–30 Hz), LSD (0.01 mg, s.c.) there was an increase in intensity and excitation frequency bands (13–100%) of the stimulated light patterns.

Brain cells

Miura *et al.* (1957), Woolley (1958 a,b), and Woolley and Shaw (1957) reported that the introduction of LSD to purely oligodendroglial cultures changes the normal rhythmic activity of these cells. Five micrograms per millimetre of LSD in a culture medium caused initial relaxation and vacuolization of cells, and finally marked contraction. The cellular response was much more pronounced at 100 μg/ml. Woolley and Shaw (1957) discussed whether the effects of LSD arise from changes in cellular metabolism. Geiger (1957, 1960) reported that LSD influences neurons (pure cell cultures). The author observed and photographed (phase-contrast microcinematography) mixed cultures and subcultures of neurons and glia over time. She reported that concentrations of 0.0002–0.001 μg/ml LSD produced marked changes (e.g. increased intracellular granulation, cell body contractions, decrease in axons and dendrites, disorderly nuclear movements, diminished Nissl substance, and oligodendroglia contractions) after 15–20 min. Chromatolysis was seen after several days of exposure to LSD. After washing out the LSD, the altered cells regenerated after half an hour. Neurons from different areas of the brain responded very differently to exposure to LSD.

Blood cells

As with many other parameters, changes to the number of circulating blood cells are also seen after administration of LSD. Belsanti (1952) reported relative neutrophilia in humans (open, crossover, $n = 14$, 80–480 μg, oral dose). Rothlin *et al.* (1956) reported elevated leucocyte counts in rats and rabbits after being given LSD (50–150 μg/kg, s.c.).

Sackler *et al.* (1963) gave rats high doses of LSD (50 or 75 μg, i.p.) on 8 different days over a period of 2 weeks. Blood was collected 24 h after the last injection. Both test groups exhibited eosinopenia—34.4% (50 μg) and 33.1% (75 μg)—and a dose-dependent, significant total neutrophilia. In both groups, there was a slight tendency towards relative lymphopenia, eosinopenia, and neutrophilia. The absolute number of lymphocytes decreased by 18.3–24.8% and that of eosinophils by 32–41.3%. The authors propose that these changes are the result of a non-specific stress response caused by the effects of LSD on the adrenal glands. In a study on female rats, Sackler *et al.* (1966) reported a significant decrease in the total numbers of leucocytes and eosinophils. Although analyses of relative frequencies of cells in differential blood counts showed a tendency towards lymphopenia, eosinopenia, and neutrophilia, statistical analyses revealed a significant decrease in absolute number of lymphocytes, but no evidence of neutrophilia. Under identical test conditions,

Weltman and Sackler (1966) examined male rats and found a dose-dependent decrease in leucocytes and eosinophils 24 h after subcutaneous injections 4–8. At 750 µg/kg LSD, the differences to the control group were significant on both days. At the lower dosage, LSD produced a smaller, but still significant decrease in leucocyte counts. However, eosinopenia was barely significant on day 4, and after 8 days no longer obvious. The authors explain these results with LSD-induced stimulation of adrenal gland function.

LSD given to rats on anticoagulant therapy was associated with haemorrhage (Lucas, 1964; Lucas & Jaques, 1964).

Hassler (1964) was able to confirm the absence of altered erythrocyte contents and number in the brain tissue of rabbits (5 mg LSD i.v.) and mice (0.03 mg LSD i.p.).

In studies on pigs, Harkonen and Konttinen (1958) reported dose-dependent relative and absolute neutrophilia as well as significant eosinopenia and mild lymphopenia. After a dose of 50 µg/kg LSD there was minimal neutrophilia, eosinopenia, and lymphopenia.

In humans, Forrer and Goldner (1951) reported that already at 1 µg/kg LSD induced leucocytosis (open, crossover, $n = 6$, 0.5–6.0 µg/kg, oral dose).

Feld *et al.* (1955) gave 15 test subjects two to six doses of LSD weekly 100 µg, p.o. After 1 week, the number of circulating eosinophilic leucocytes decreased by more than 40%. These findings have not be confirmed by other authors, either in humans ($n = 4$) with (5-100 µg, p.o.) (Lovell *et al.*, 1953) or in rats (Milkovic & Supek, 1956).

According to Hollister and Sjoberg (1964), the number of circulating eosinophilic leucocytes tends to show a very slight, decrease within the first 2 h after administration of LSD (double blind, crossover, $n = 24$, 1.5 µg/kg, oral dose).

Oxygen consumption

In vitro studies on pig and rat brain preparations yielded contradictory results with regard to oxygen consumption after the administration of LSD (Mayer-Gross *et al.*, 1953; Starbuck & Heim, 1959; Geronimus *et al.*, 1954; Lewis & McIlwain, 1954; Broer *et al.*, 1963).

Hertle *et al.* (1962) compared basic metabolic rate and oxygen consumption in test subjects before and after administration of LSD (open, crossover, $n = 6$, 1 µg/kg, i.v.), with results showing strong mean variation. While hyperventilation could explain the increased metabolic rate, it was only observed in half of the test subjects. On the whole, the findings indicated that LSD leads to an increase in energy metabolism; however, these data did not offer clues as to direct metabolic effects.

Biochemical changes

Carbohydrate metabolism

Carbohydrate metabolism was initially considered a potential source of the psychopharmacological effects of LSD (Mayer-Gross *et al.*, 1951). However, more precise studies on humans have shown only minimal effects (Freedman & Boggan, 1982; Lajtha, 1958).

In one study, 24 people were tested after being given LSD (single blind, crossover, $n = 24$, 20–60 μg, oral dose) on an empty stomach. Tests showed that lactate and pyruvic acid levels were within normal ranges, but that blood glucose levels were elevated by about 15 mg/100 ml after 1 h and hexose monophosphate levels were also significantly changed. In a follow-up experiment under identical test conditions, psychological and physical symptoms of LSD intoxication subsided noticeably after i.v. administration of a 33% glucose solution. It was thus proposed that LSD blocks the break down of hexose monophosphate (Mayer-Gross *et al.*, 1952). A study with 13 fasting subjects showed decreasing levels of hexose monophosphate in the blood, which markedly increased after the administration of LSD (open, crossover, 80μg, oral dose) (Mayer-Gross *et al.*, 1953). Anderson and Rawnsley (1954) reported reduced oral glucose tolerance in subjects under the influence of LSD (open, crossover, $n = 23$, 10–600 μg, oral dose). Sokoloff *et al.* (1956/1957) found no aberrations in glucose utilization after administration of LSD (open, crossover, $n = 41$, 120 μg, i.v.). This was confirmed by Ellis (1951) and Hollister and Sjoberg (1964).

Studies on rats showed that LSD significantly inhibits cerebral phosphorylase activity (Iriye *et al.*, 1963, 1965). Torre and Vergani (1969) reported increased glycolysis in the brains of rats 1 h after LSD injection. Experiments by Rothlin (1956) and Konzett (1956) on rabbits confirmed a dose-dependent increase in blood sugar levels after administration of LSD. However, following further studies with other centrally and peripherally active substances (e.g. hexamethonium), Konzett interpreted this as a symptom of general central stimulation of the sympathetic nervous system. This was confirmed by Elder (1964) in experiments on cats. Berenstein and Otero (1958) reported mild hyperglycaemia in dogs, 2–6 h after 100 μg/kg LSD .i.v.

In addition to these *in vivo* studies, several *in vitro* studies have also been conducted. At very low concentrations (4×10^{-9} M), a decrease in glucose-1-phosphatase and an increase in glucose oxidation could be observed (Mayer-Gross *et al.*, 1953).

At rather low concentrations, no change was detected in oxygen consumption in brain and liver mitochondria in pigs (Bain, 1957). Bender and

Siva Sankar (1968) reported increased cerebral glucose oxidation and diminished oxidation in cerebellar homogenates: citrate, succinate, and γ-amino butyric acid–glucose oxidation were elevated in both homogenates. Using rat brain preparations, Torre and Vergani (1969) showed significant dose-dependant inhibition of glycolysis. Phosphorylase and hexokinase activities were not influenced.

Given that test conditions can vary so greatly between studies, it is difficult to compare results on carbohydrate and glucose metabolism (Giarman & Freedman, 1968; Hoagland, 1957).

Calcium metabolism, phosphate metabolism, and creatinine clearance

In rats, LSD (500 μg, intraperitoneal administration) has been shown to cause diminished phosphate excretion without altering urine creatinine levels (Siva Sankar *et al*., 1962b).

Phosphate excretion after the administration of LSD (25 μg) and ACTH has been measured in studies on pigs. Phosphate levels in 24 h, around-the-clock urine collections were within normal ranges after 10 h. However, at double the amount of LSD, phosphate excretion was inhibited by up to 47%; at 100 μg LSD it was inhibited by only up to 20%; and at greater doses, there was no effect at all. When ACTH was given alone, phosphate excretion remained unchanged. When it was given in combination with LSD, it blocked its effect on phosphate metabolism. Phosphate excretion can be seen to increase however, when ACTH is given after LSD has been administered (Bergen & Beisaw, 1956).

In humans, LSD (0.5–1 μg/kg, p.o.) has been shown to reduce excretion of anorganic phosphate. This led early on to the belief that LSD interacts with enzyme systems, which promote phosphate binding (Pincus & Hoagland, 1950). Hoagland *et al*. (1955) showed a marked reduction in anorganic phosphate levels in urine 6 h after subjects were given LSD (open, crossover, $n = 12$, 0.5–1.0 μg/kg, p.o.). The combination of LSD and ACTH (25 mg) led to increased phosphate excretion. Similar results were reported with schizophrenic patients who received ACTH. Normal subjects had no change in phosphate levels after being given ACTH. This study appears to indicate stimulation of the hypophyseal–adrenal axis by LSD. Hollister and Hartman (1962) reported diminished excretion of anorganic phosphate in study subjects (open, $n = 12$, 1 μg/kg, p.o.). Rinkel *et al*. (1955) showed a marked reduction in phosphate excretion in subjects after administration of ACTH and LSD (open, controlled, $n = 15$, 0.5 μg/kg, p.o.). In a study by Bender (1966), schizophrenic children were given single doses of 100 μg LSD over a period of several weeks. Elevated anorganic phosphate levels were detected in erythrocytes within the first hour after LSD

was administered. In 70% of the children, an increase was observed as the drug began to take effect and in 29% it was seen later.

Although the drop in an organic phosphate excretion is certainly relevant, its significance in the search for the mechanism of how LSD works is unclear. A reduction in excreted phosphate could be viewed as a result of oliguria triggered by LSD (Graham & Khalidi, 1954). The slight increase in respiration after taking LSD may also partly explain this finding. To compensate (acid–base equilibrium), there would be a decrease in excretion of acids (Katzenelbogen & Fang, 1953). It is more likely, however, that it represents a non-specific reaction to a sympathomimetic syndrome. Forrer and Goldner (1951) reported that after six daily doses of LSD (open, controlled, $n = 6$, 1 μg/kg, p.o.) no changes were detectable in urine analyses done over a 14-day follow-up.

Hollister and Sjoberg (1964) reported a significant decrease in creatinine clearance in subjects who were given LSD (double blind, crossover, $n = 24$, 1.5 μg/kg, p.o.).

Fatty acids

A typical effect of hallucinogenic substances is the mobilization of fatty acids (Hollister & Hartman, 1962). Two hours after LSD administration (1 μg/kg, oral dose) a highly significant rise in fatty acids can be observed. At a dose of 1.5 μg/kg LSD (double blind, crossover, $n = 24$, oral dose), peak elevation of free fatty acids occurs at 4 h, although at higher doses the level at 2 h remains the same, when compared with the previous trial (Hollister & Sjoberg, 1964). In the search for parallels to adrenaline (3 μg/kg, subcutaneous dose) in fatty acid mobilization, it was reported that LSD (randomized, crossover, $n = 49$, 2 μg/kg, subcutaneous dose) has a similarly strong, but more gradual and prolonged increase. Considering that placebo also leads to a slight increase in free fatty acids, this phenomenon is probably best understood as part of a general activation of the sympathetic nervous system (Hollister & Moore, 1965, 1967).

Serum triglyceride levels reportedly remained normal after subjects were given 1.5 μg/kg LSD p.o. (Hollister & Sjoberg, 1964).

Cholinesterase activity

After it was discovered that acetylcholine levels increased in the brains of pigs who were given LSD, some researchers began investigating the role of cholinesterase in the mechanism of hallucinogenic action (Poloni & Maffezzoni, 1952; Nandy & Bourne, 1964; Nandy *et al*., 1964; Kabes & Fink, 1969; Freedman & Boggan, 1982).

In fact, pseudoesterase was proved to inhibit by 50% in preparations of human brain tissue. This finding was of limited use however. Cholinesterase is involved in neuronal and brain functions, yet even at 10 times the dose of LSD, it is only inhibited by up to 10%. Compared with other esterase inhibitors, LSD has a highly specific effect, mainly on pseudoesterase. While this may explain the accumulation of acetylcholine in the brain, whether it is important in explaining the mechanism of action of LSD is questionable (Thompson *et al*., 1955). Greig and Gibbons (1959) reported a diminished penetration of radioactive ^{14}C-glucose under LSD in rat brains. They suspected that it resulted from an inhibition of cholinesterase, causing relative glucose deficiency. Zsigmond *et al*. (1961) studied the inhibitory effect of LSD on human cholinesterase in serum, grey matter, and erythrocytes. Serum cholinesterase was more strongly inhibited than other cholinesterases. No correlation was evident between *in vitro* acetylcholinesterase activity and hallucinogenic or anti-serotonergic activity of individual components. To study acetylcholinesterase activity *in vitro*, Bajgar *et al*. (1971) prepared four human brains in such a manner that the individual cell components of the head of the caudate nucleus were accessible. The bulk of the acetylcholinesterase that was inhibited by LSD was present in the microsomes, followed by the rest in cellular debris and mitochondria. The relevance of these findings for human pharmacology is debatable, however. At 2.5×10^{-6} M LSD, 10% of acetylcholinesterase is inhibited, which corresponds to a dose of 140 mg/70 kg. The authors therefore ruled out the possibility of a primary contribution to the psychotomimetic effects of LSD by acetylcholinesterase inhibitors.

Similarly, other authors have reported that LSD can inhibit cholinesterase *in vitro* (Zehnder & Cerletti, 1956; Fried & Antopol, 1957; Tabachnick & Grelis, 1958; Foldes *et al*., 1959; Goldberger, 1961; Ruckenbusch *et al*., 1966). Goldberger (1961) suggested that the psychological effects of LSD may be partly due to the uncontrolled diffuse stimulation of brain cells arising from markedly elevated acetylcholine levels. Other research groups reported inhibition failing to happen or even leading to a mild activation of the enzyme by the LSD (Tonini, 1955; Fried & Antopol, 1957; Bertino *et al*., 1959a).

Rat studies have demonstrated an inhibition of specific cholinesterase and monoamino oxidase (MAO) in the liver after LSD administration (0.1 mg/kg, i.v., i.p. or intracardiac). Inhibition of cholinesterase by these substances was more evident in the liver lobules than in central veins. MAO was inhibited equally throughout the liver specimen, and its inhibition was comparatively stronger than that of cholinesterase (Nandy & Bourne, 1964a). In neurons of the spinal ganglia of the dorsal horns of the spinal cord, LSD also diminished the levels of specific cholinesterase and MAO. The authors suggest that such

changes could lead to a higher impulse input, overloading the CNS (Nandy & Bourne, 1964b). Shanthaveerappa *et al.* (1963) also reported inhibition of MAO and cholinesterase in rats given LSD (0.1 mg/kg, i.v., intraperitoneal or intracranial administration). The inhibitory effect was the greatest in brainstem nuclei and in the thalamus. The highest density of both enzymes was also found there. It has been suggested that LSD leads to inactivation of cholinesterase and MAO and thus inhibits the breakdown of acetylcholine and adrenaline, which influence synaptic impulse transmission. The extensive inhibition of cholinesterase in the thalamus and brainstem nuclei could lead to such an abundance of these transmitters, causing the cerebral centres to be inundated with impulses from a subcortical level.

Others

Callieri and Mariani (1957) gave test subjects LSD (open, crossover, $n = 4$, 120 µg, i.v. administration) and observed a reduction in serum alkaline phosphate activity of around 26%. The activity of acidic phosphatase dropped by 43%.

Analgesic effects

The idea of using LSD as an analgesic, as proposed by Kast and Collins (1964), was based on the notion that it alters perception and integrity of the body scheme in such a way that pain is pushed out of the central focus of conscious experience. The authors investigated the analgesic effects of dihydromorphine and meperidine and compared them in a double-blind study with LSD. Each of the three substances was tested on severely ill pain patients ($n = 50$) with various diseases (mainly cancer). The effects were then measured subjectively and objectively. The results showed that there was a comparably long delay before LSD (100 µg) took action, but that it had a strong analgesic effect. Undesirable effects (e.g. nausea and vomiting) were more frequent with the traditional analgesics, and the psychological effects of LSD were perceived as only mildly bothersome.

A comprehensive summary of the experiences with LSD therapy in terminally ill patients was published in *The Human Encounter of Death* (New York: E.P. Dutton, 1977), by Grof and Halifax. Along with Kast and Collins (1964), Cohen (1965), Pahnke *et al.* (1970) the authors are considered pioneers in this use of LSD.

Allergic reactions

There are as yet no reports or observations of allergic reactions to LSD in human beings.

During an anaphylactic reaction, there is a massive increase in serum serotonin and ATP. This has led some to suggest that LSD could conceivably influence

anaphylaxis. In studies on pigs which were sensitized with cattle serum, Pallotta and Ward (1957) confirmed a protective effect of LSD (1–100 μg/kg) against anaphylaxis. Since a study by Graham & Khalidi (1954) demonstrating that there is no antihistamine effect, serotonin is believed to be responsible for anaphylaxis.

In a study by Shibusawa *et al.* (1958), dogs and pigs were sensitized with horse serum and then re-exposed to it to induce an anaphylactic reaction. Ten minutes before the shock-inducing injection, the animals were given LSD (10 μg/kg i.m.). In some of the dogs, this prevented a fatal shock, although mortality among the pigs was high. LSD caused a sharp drop in blood pressure and thrombocytopenia. There was a comparatively strong increase in serum ATP and histamine concentrations. Only serotonin levels showed a mild increase. When the dogs were given both LSD and ATPase, blood pressure levels and respiration rates remained nearly normal. Increases in serotonin and ATP were avoided. Fatality was prevented in 40% of the pigs.

Fox *et al.* (1958) sensitized mice with horse serum. When the animals were given LSD (56–100 μg, i.v.) 2 h before re-injection of the serum, LSD had a protective effect against anaphylaxis without any observable sedation. O'Brien *et al.* (1962) observed anaphylactic reactions (induced by dextran or protein) in which serotonin was involved. The authors showed that LSD had a positive influence on experimentally induced allergic encephalitis. Even at doses of 50 μg LSD three times a week, the incidence of paralysis was reduced, as were mortality rates and the severity of histopathological lesions detected in pigs with allergic encephalitis.

Immune system

House *et al.* (1994) examined LSD-induced modulation of the immune system after direct *in vitro* exposure. At concentrations of 100 μM, LSD suppressed the proliferation of B lymphocytes. Furthermore, the production of cytokines interleukin (IL)-2, IL-4, and IL-6, as well as the induction of cytotoxic T lymphocytes, was inhibited. *In vitro* LSD exposure of natural killer (NK) cells yielded various results, depending on dosage level. At low concentrations (0.0001–0.1 μM) LSD enhanced both basal and IL-2 augmented NK cells, while at 100 μM there was a suppression of NK cells. This implies that LSD (in doses not considered clinically relevant) has a direct effect on components of the immune system.

Carcinogenicity

Soon after use of LSD started becoming more widespread among Americans, a discussion started on its potential carcinogenic effects. Such speculations were

first published by Cohen *et al*. (1967a), based on observations of a higher frequency of chromosomal aberrations in a schizophrenic patient after LSD psychotherapy.

This hypothesis was supported by Irwin and Egozcue (1967), who had discovered chromosomal fragments in nine LSD users. The fragments strongly resembled the Philadelphia chromosome (seen in chronic lymphatic leukaemia [CML]).

Dishotsky *et al*. (1971) reported on three retrospective studies in which long-term chromosomal damage was seen after LSD use. In two prospective studies, detected changes later disappeared. Moreover, the chromosome resembling the Philadelphia chromosome was found in only two studies. In both studies, it was located in peripheral leucocytes. Yet in CML such changes are restricted to bone marrow cells.

Garson and Robson (1969) described two patients with leukaemia after consumption of pure LSD. Nevertheless, the onset of disease in both patients may be coincidental.

The early findings reported by Cohen *et al*. (1967a) have been often cited as evidence of the possible carcinogenic potential of LSD. Yet the results have never been reproduced.

Given that in thousands of serial administrations of LSD there has been no increase in the frequency of malignancy, and that its carcinogenic potential is anecdotal at best, one may conclude that LSD possesses only minimal carcinogenic potential, if any (see Grof, 1980 for a complete review).

Effect on chromosomes and embryotoxicity

Effects of LSD on chromosomal structures

The possible damage to genetic material caused by artificial influences (e.g. radiation exposure, viruses, and chemical substances) has long been discussed. In 1967, Cohen *et al*. (1967a) postulated a relationship between LSD and chromosomal damage. The topic sparked a large amount of interest, given the widespread use of LSD.

In vitro studies

Egozcue and Irwin (1969) collected blood samples from six male and six female rhesus monkeys and incubated the specimens with 1 μg/ml LSD. Cultures treated with LSD had an average breakage rate of 29.4% (controls: 11.8%).

Cohen *et al*. (1967b) incubated leucocytes from six study subjects for 4, 24, and 48 h after adding various amounts of LSD (0.001–10 μg/ml). The rate of chromosome breakage was twice as high in cells treated with LSD. Yet no straightforward relationship was found between dose or incubation time and

the extent of chromosomal aberrations. Among controls, the lowest frequency of chromosomal aberrations was 3.9%. In cells incubated with LSD, it was twice as high (7.7%), up to a maximum of 17.5%. These results were never reproduced.

Jarvik *et al*. (1968) studied leucocytes, which were incubated with LSD (0.01 μg/ml). The authors reported a breakage rate of 10.2% (controls: 5.2%).

Hirschhorn and Cohen (1968) examined lymphocyte cultures from six healthy subjects. LSD (0.001–10 μg/ml) was added and the cultures incubated. At all dosages and exposure times, the addition of LSD led to an increased number of abnormal cells (e.g. chromatid and isochromatid breaks, chromatid exchange, and dicentric chromosomes), ranging from 3.8% (controls) to more than three times as high.

In other studies, leucocytes from 10 subjects were incubated for 24 h with LSD (1 μg/ml). Despite the high dose, the breakage rate was only 4.65% and thus comparably low (controls: 0.0–15.2%; Corey *et al*., 1970).

Other researchers have not found any evidence of an increased rate of breakage related to LSD (MacKenzie & Stone, 1968; Sturelid & Kihlman, 1969), although they selected comparably high doses and incubation times.

In studies on isolated human umbilical cord (Gant & Dyer, 1971) or placenta (Astrom & Samelius, 1957), LSD had serotonergic vasoconstrictive properties and led to relaxation of smooth muscle cells. After administering LSD alone, it exhibited a strong vasoconstrictive effect (90% of serotonergic potential). Gant and Dyer (1971) thus hypothesized that LSD disrupts placental transfer during pregnancy.

In vivo studies

Dishotsky *et al*. (1971) presented a summary of test subjects prior to 1971. Of a total of 310 study subjects, 126 had received pure LSD. The second group (n = 184) had received impure LSD, and some had also consumed other substances. In the first group, 14.29% had a higher rate of chromosomal aberrations than the control groups. Yet in the second group, 89 (48.9%) of people had increased incidence of aberrations. It should be noted, however, that consumption of other substances was not documented in detail. This could be one possible explanation for the higher rate of aberrations.

Impure LSD and chromosomal damage

There are a number of studies on impure LSD and chromosomal damage. Yet due to poor methodology and lack of documentation of concomitant consumption of other substances as well as co-morbidities, the results are inconclusive (Cohen *et al*., 1967, 1968; Irwin & Egozcue, 1967; Egozcue *et al*., 1968; Hirschhorn & Cohen, 1968; Nielsen *et al*., 1969).

Other researchers using similar approaches have found no evidence of increased rates of chromosomal aberration (Loughman *et al*., 1967; Hulten *et al*., 1968; Sparkes *et al*., 1968; Jarvik 1969; Judd *et al*., 1969; Lucas & Lehanbecker, 1969; Dorrance *et al*., 1970).

Such contradictory results invite consideration of potential sources of error. Viral contamination of specimens, technical variation between test groups, and failure to distinguish between chromosome and chromatid changes could all produce discrepancies. Yet even these factors do not fully explain the discrepancies described above. Other explanations, apart from factors directly related to experimental procedure, may therefore be worth considering. All study subjects consumed various other substances in addition to LSD. The interactions and the effects of these on human genetic material are largely unknown (ritalin, phenothiazine, alcohol, amphetamine, cocaine, barbiturates, heroin and other opiates, cannabis products, psilocybin, mescaline, DOM, methylenedioxyamphetamine (MDA) or DMT). The higher rate of malnutrition, venous disease, as well as hepatitis and other viral diseases in this group should also noted. All of these factors should be considered in a discussion of possible events leading to chromosomal damage.

Pure LSD and chromosomal damage

The following chromosome studies examined results from subjects who were given pure LSD in unknown amounts and frequencies as part of psychotherapy treatment or within the framework of controlled experiments.

Nielsen *et al*. (1968) examined leucocytes from five patients who were given up to a total of 17.5 mg LSD over 6–38 months for therapeutic purposes. The researchers discovered an increased number of breaks ($p < 0.01$), gaps ($p < 0.001$), and hyperdiploid cells ($p < 0.01$) compared with 40 controls. In another study by Nielsen *et al*. (1969), there was an increased breakage rate of around 4.3% in a group of nine patients who had used LSD. Dishotsky *et al*. (1971) criticized the findings, however, citing highly questionable statistical analyses.

Sparkes *et al*. (1968) reported no chromosome breakages in four patients who were treated with LSD (250–500 µg per weekly session over 12–48 months).

In another study, the chromosomes of 15 children with psychiatric problems were examined after administration of LSD, methysergide (UML), or a combination of the two substances. Each patient was given an average 142.4 µg LSD daily (treatment duration: 2–1366 days). In the LSD group, the breakage rate was 0.8% and among patients on combination therapy it was 1.0%. This was not significantly higher than in controls (Sankar *et al*., 1969).

Tijo *et al.* (1969) published results of a study with eight healthy individuals. Subjects received 1–26 doses per patient LSD (controlled, double blind, total doses: 300–4800 μg) in experimental settings and 2–5 months before a blood sample was taken. The average rate of chromosomal aberrations was 2.8%, and thus not significantly greater than that of controls. The authors compared these results with those of lymphocyte studies before and after LSD was given to 32 patients in hospital psychiatric wards. Dosage ranged from 50 μg LSD in 11 patients to 250–400 μg in the remaining 21 (controlled, double blind, oral dose). Again, no statistically relevant increase was seen in chromosomal breakage.

Robinson *et al.* (1974) designed a study with psychiatric patients (controlled, $n = 100$) in which 50 patients received weekly injections of LSD (first week 50 μg, continually increasing by 50 μg per week to 400 μg, i.m.). Chromosome studies were conducted up to 12 months post-injection. No statistically significant differences were seen in the lymphoid cells of treated patients versus control subjects.

Corey *et al.* (1970) found no increase in frequency of chromosomal aberrations in people who were given LSD (crossover, $n = 10$, 200–600 μg, oral dose).

Tijo *et al.* (1969) reported on 32 hospitalized patients who received LSD in a double-blind study at Maryland Psychiatric Research Center. Ten patients received individual doses of 50 μg LSD and 22 patients received 250–400 μg LSD. The number of examined cells (22,500) was more than double that from all previous studies. Surprisingly, the number of chromosome breaks was higher in the group, with a lower dose of LSD than in the other group.

Bender and Sankar (1968) found no chromosome abnormalities in 27 autistic children treated with 100–150 mcg LSD daily for up to 2–3 years.

Reviews by Grof (1980), Smart and Bafeman (1968), and Long (1972) concluded that LSD does not cause chromosome breakage and is not a teratosen.

Chromosomal changes in germ cells

The results of chromosome studies on peripheral blood cells have led to far-reaching speculations on the possible influence of LSD on germ cells.

After exposing meiotic cells in rodents to massive amounts of LSD, several researchers have described various severe chromosomal aberrations (e.g. Cohen *et al.*, 1968b; Shakkebaek & Beatty, 1970; Shakkebaek *et al.*, 1968).

Egozcue and Irwin (1969) examined rhesus monkeys after a single dose of LSD (5, 10, 20, or 40 μg/kg) and 6 months later in weekly intervals after four doses of LSD (controlled, $n = 4$, 40 μg/kg, oral administration). Half of the monkeys had increased chromosomal breakage rates in cell samples taken from the testes.

Yet despite fulminant LSD exposure, other researchers have found no evidence of increased breakage rates in the germ cells of mice (Egozcue & Irwin, 1969; Jagiello & Polani, 1969) or fruit flies (Grace *et al*., 1968; Markowitz *et al*., 1969).

Given the considerable differences between the species, these results are not necessarily applicable to human beings.

The only report on the effects of LSD on human gametes is by Hulten *et al*. (1968). In this study, the authors examined germ cells from a testicular biopsy taken from a patient who had consumed high amounts of LSD for many years. His self-reported consumption sometimes reached 1000 μg daily for 4 weeks. No evidence of sperm cell damage was found. In summary, evidence on a potential influence of LSD on gametes is still inconclusive. Even at sometimes very high doses, no changes have been detected.

Mutagenic effects of LSD

Tests on animals Studies have been undertaken on animal and plant cells to determine the mutagenic potential of LSD. However, no experiments have been carried out on human cells.

On fruit flies, even very high doses (400–4000 μg/kg) had only a weak mutagenic effect (Browning, 1968; Grace *et al*., 1968; Markowitz *et al*., 1969; Vann, 1969; Vann *et al*., 1970). Bick (1970) investigated this in the blood from rat kangaroos (*Potorous tridactylus*, long-nosed potoroo) given different doses of LSD (0.4–6.64 μg/ml). As doses increased, an increase in chromatid and isochromatid deletions could be observed. All chromosome exchanges found were of the chromatid type. From these observations, the author concluded that LSD affects the chromosomes during the synthesis (S) or post-synthesis (G_2) phase, since an exchange only occurred in the chromatids. Accordingly, chromosome damage through LSD cannot be proved in blood cells, since those are not involved into the division cycle any more. Goetz *et al*. (1973) examined the mutagenic activity of LSD (10–1000 μg/kg, i.p.) in cytological analyses of primary rat and mouse spermatozoa and by means of the 'dominant lethal test'. Compared to controls, only small numbers of chromosome breaks were found and no rearrangements. The number of spermatozoa with normal chromosomes decreased only on rats, which had been treated with 1000 μg/kg LSD, an overdose of about 1,000 times. Repeated doses also influenced the fertility of the animals treated.

Many scientists have assumed that LSD might have a negative effect on prenatal development and might lead to abortions and malformations. Since autoradiographic studies by Idänpään-Heikkilä and Schoolar (1969), which proved the free transfer of LSD through the placenta of guinea pigs, such an assumption seemed plausible.

Comparable studies on mice, rats, and guinea pigs, however, brought up inconsistent results. Auerbach and Rugowski (1968) described an increased appearance of brain damage in mice embryos after an exposure to LSD (1×10^{-6}–5×10^{-8}, i.p.) in the womb. Geber (1967) and DiPaolo *et al.* (1968) treated pregnant guinea pigs with LSD (0.0008–0.24 mg/kg, s.c. or rather 10–300 μg, i.p.). They described an increased incidence of stunted growth, stillbirth, and ZNS changes. Hanaway (1969) observed a high incidence of abnormalities on mice lenses after the mice had been fed with LSD (5×10^{-6} g, i.p.) for several days. Alexander *et al.* (1967) and Nosal (1969) reported an increased frequency of stillbirth and shuntings during early pregnancy (5 μg/kg, s.c., or rather 5–1000 μg/kg, i.p.). Treatment with LSD during the first 7 days had severe consequences. After this time, however, the substance did not cause any more damage. The LSD effects on the foetus seem to be dependent on the dose and persist to the second generation. The LSD transferred through breast milk did not lead to any pathology on the newly born (Alexander *et al.*, 1970).

Despite high doses (1.5–300 μg, i.p. or p.o.) Warkany and Takacs (1968) as well as Beall (1972) and Sato *et al.* (1971) could not observe any abnormalities in rats. The rate of mortality rate and deformation in rabbits (20–100 μg/kg, p.o.; Fabro & Sieber, 1968), mice (5–500 μg/kg, s.c.; Roux *et al.*, 1970), rat (500 μg/kg, i.p.; Roux *et al.*, 1970; Emerit *et al.*, 1972) or chicken embryos (10–70 μg per egg; Bargman & Gardner, 1974) also was not significantly higher than in the controls.

During the only experiments with primates, Kato and Jarvik (1970) injected multiple doses of LSD (50–100 μg/kg, s.c.) into pregnant rhesus monkeys. One out of four animals treated gave birth to a healthy infant, two had stillbirths with deformations of their faces, and the fourth newly born died after 1 month. The doses applied here correlated with 100 times the clinically relevant dose for humans.

In a discussion on the results of animal experiments to determine the mutagenic or, respectively, teratogenic potential of substances, it is first of all worth mentioning that the animal studies referred to here have, without exception, all been carried out with massive overdoses—compared to the usual human doses of LSD—and therefore are more like toxicity studies.

Also, the argument of interspecies scaling, which bases on the assumption of a higher risk at equal dosage in more complex animal species, is—if at all—only applicable in a very limited way, considering the many findings contradicting this principle.

Human Casuistics In scientific literature, there are a number of single-case casuistrics on a probable correlation between LSD and malformations of the newborn. They have also been completely investigated in the framework of

this presented work. They are, however, marked by totally individual medical backgrounds in the single cases and only refer to the consumption of impure street LSD under uncontrolled conditions.

There are no reports on malformations in patients, who, under controlled conditions, had been given LSD, although the like has been observed (Leuner, 1981). However, the cases in which such a connection has been inferred have been rarely reported, if one considers the worldwide and not insignificant extent of LSD consumption. After looking at these studies, no two identical cases of malformation appeared whatsoever, which means definitely that no LSD-specific form of malformation was reported.

According to the reasons mentioned, no scientifically proven evidence can be found in the available scientific literature, for any mutagenic or teratogenic potential in the usual doses taken for human consumption (including multiple overdoses). In order to help access, the casuistics have nevertheless been listed (Zellweger *et al*., 1967; Abbo *et al*., 1968; Hecht *et al*., 1968; Sato & Pergament, 1968; Arendsen-Hein, 1969; Carakushansky *et al*., 1969; Egozcue, 1969; Assemany *et al*., 1970; Berlin & Jacobson, 1970; Eller & Morton, 1970; Hsu *et al*., 1970; McGlothlin *et al*., 1970a; Warren *et al*., 1970; Blanc *et al*., 1971; Dumars, 1971; Bogdanoff *et al*., 1972; Jacobson & Berlin, 1972; Pilapil *et al*., 1973; Goodman & Gilman, 1975; Chan *et al*., 1978; Von Mandach *et al*., 1999).

Impacts on the infant's sex

Aase *et al*. (1970) observed a group of 10 pregnant women who had consumed LSD. All women gave birth to 10 live and healthy children (without teratogenic or chromosome damage). The only striking feature lay in the fact that all children were of the female sex. Since the probability for such an event is 1:1024, one could assume that LSD is able to influence the sex of the unborn. Healy and Van Houten (1970) speculated that LSD could be in the position to magnify an immunological incompatibility between male foetuses and their mothers. Healy's (1971) investigations on the effects of psychoactive substances on the sex of mice descendants looked in a similar direction. On the fifth day of pregnancy, s.c. the animals were inoculated with LSD, normal leucocytes, normal plasma, as well as leucocytes and blood plasma from schizophrenic patients and placebos. Owing to a lack of significant differences between the single groups, the author concluded that observations were human-specific.

Influence on the sleep–awake cycle and dream experience

During the 1960s, a serotonin-dependent biochemical chain reaction was discovered, which modified the synaptic transmission in cholinergic structures of

the hippocampus, apparently influencing theta activity and dreaming. Experiments showed that increased serotonin content in the brain extended the length of time spent dreaming during the night (a.o. Oswald, 1965; Dement, 1966), whilst lowered concentrations of seratonin could shorten dreamtime (Matsumoto & Jouvet, 1964).

Hobson (1964) examined the effect of LSD on the sleeping cycle of cats and was able to show that moderate doses influenced sleep in a non-specific manner and low doses reduced low-voltage fast sleep (LVFS). This was confirmed on eight cats with chronic electrode implants (LSD: 2 and 20 μg/kg, i.p.). It was possible to observe a strong reduction in the percentage duration of the LVFS and also premature awakening. A dose of 20 μg/kg LSD did not reduce these parameters significantly, while it was possible to see a significant reduction in the duration of the LVFS after the application of 2 μg/kg. The latency until the beginning of the first LVFS doubled under LSD, but the total period awake, or the time until sleep occurred, did not change significantly. In the nights after LSD application, there was a definite increase in LVFS.

The first experiments on the influence of LSD (open, $n = 3$, 25 μg, p.o.) on sleep in humans showed signs of increased restlessness and extended REM phases (Toyoda, 1964). A similar experiment was carried out on a young patient (alcoholic, anamnesis; no psychosis or delirium). EEG measurements were made in the two nights proceeding LSD administration, during administration (open, $n = 1$, 300 μg) and in the following two nights. First of all, it was noticed that the start of the first REM phase was significantly delayed. The duration, as well as the percentage share of the REM phase during the complete period of sleep, was increased in the LSD night and in the following night even more so. Parallel to this, during these nights, there was significantly more body movement, more noises were emitted, and a higher galvanic skin resistance could be measured. Isolated, single bursts of REM, which were not observed during the previous nights, appeared only on the night of LSD administration and the following nights. The suspected increase in dream duration under LSD was thus confirmed (Green, 1965, 1969).

Muzio *et al.* (1966) administered LSD (single blind, crossover, $n = 12$, 6–40 μg, p.o.) either shortly before sleep or 1 h after sleep had begun. On these nights, it was possible to see an extension of the first or the second REM phase. After an extended REM phase, the next phase was always a shortened one, but thereby the absolute REM period was also extended. Furthermore, the phases of slow-wave sleep were interrupted by characteristic short REM bursts and increased body movement, plus sudden awakening during the REM phase. To summarize, it can be said that LSD extends REM phases and the total period of REM activity and can promote sudden awakening, depending on the dose.

Torda (1968) took EEG activity data from two test persons during 10 consecutive nights. During three of those nights, LSD (open, crossover, $n = 2$, 5 µg/min., i.v.) or placebo were infused at different times after the beginning of the third REM phase. The result found was that LSD decreased the latency of the next REM phase to 10–19 min (placebo: 40–60 min). After LSD infusion, there was an increase in fluctuation of the theta waves.

Effects of LSD during sleep deprivation

In the 1950s and 1960s, experimental proof was found that sleep deprivation leads to measurable cerebral changes and to psychotic experiences and behaviour, along with conditions of confusion (Hinkle & Wolf, 1956; West *et al.*, 1962).

The first experimental study on sleep deprivation and LSD was carried out by Bliss *et al.* (1959). In the first part of the experiment, healthy test persons received one dose of LSD ($n = 4$, 0.5 µg/kg, no information on study design and mode of application). On another day, the dose was doubled. The test persons only noticed any effect from the LSD after the higher dose. In the second part of the study, they were not allowed to sleep for 48 h and were then given 0,5 µg/kg LSD. The hallucinations which appeared with this dose, one which did not work hallucinogenically in the first round, was described as more intense than at 1.0 µg/kg. Safer (1970) gave test persons LSD (single blind, controlled, $n = 33$, 1.5 µg/kg, p.o.) or placebo after a night without sleep. The second group spent a night without sleep and then received LSD. The remainder of the people had no sleep for two nights. The result of clinical tests showed no great differences between the third group and the control group. Only the Number Facility Test (part of psychometric measurements, after Moran & Mefferd, 1959) was significantly worse in all points, and it showed up weaknesses in vigilance and the accuracy of perception.

Tolerance and cross-tolerance

Tolerance is defined as an acquired change in the ability of the body to react, as a result of the repeated application of pharmacologically active substances. Because of this, a higher dose is needed when the drug is taken again, in order to induce an equally strong effect as the first dose. Numerous researchers were able to prove the development of tolerance in humans with the classic hallucinogenics such as LSD, mescaline, and psilocybin (Cholden *et al.*, 1955; Isbell *et al.*, 1955; Abramson *et al.*, 1956; Isbell *et al.*, 1956; Hoffer and Osmond 1967; Hollister *et al.*, 1969; Angrist *et al.*, 1974). It was apparently not easy to demonstrate the development of tolerance with hallucinogens, because these

are dependent on exact measurements and carefully controlled doses and time intervals, which were not all available in the 1950s and 1960s. This is why the groups of researchers produced diverging results.

Tests on animals Some autonomous effects of LSD (mydriasis, hypothermia, hyperglycaemia, and saliva and tear flow) show tolerance development in rats (Rothlin & Cerletti, 1956). Freedman *et al*. (1958) used the 'the interruption of rope climbing on the way to food' in rats as an examination index. At 130–260 μg/kg LSD i.p., tolerance developed within 4 days of daily application. By contrast, an application of 130 mg/kg LSD at an interval of every 48 h for 14 days resulted in only a partial tolerance. The same dosage of LSD with an interval of 72 h for 14 days did not lead to tolerance development in rats. Mahler and Humoller (1959) injected rats with a daily dose of 0.3–0.7 mg/kg LSD i.p. and observed a prolongation of climbing time. After a few days of administration, a tolerance for these indices appeared and the time taken to reach the target returned to normal.

Gillett (1960) investigated the development of tolerance on the sexual behaviour of rats. After the administration of LSD (130 μg, i.p.), a reduction in the number of copulation attempts with ejaculation was observed. Three injections of LSD at intervals of 92 h did not influence this phenomenon.

Tolerance development was also absent in Hamilton's (1960) investigation of the running speed of rats (flight from a shock situation). A constant increase in the running speed was observed with seven injections of LSD in increasing doses (0.13–1.0 mg/kg, i.p. on consecutive days).

Both d-LSD (0.195 mg/kg, i.p.) and l-LSD (1.3 mg/kg, i.p.) led to partial tolerance in rats after 7 days of daily doses. Bar-pushing behaviour (positive reinforcement) returned to 80% of its initial value after 5–6 days (Appel & Freedman, 1968). Bignami (1972) was not able to find any tolerance in rats towards the effects of LSD, after 4 days of injections of LSD (0.05–0.2 mg/kg, i.p.). Stoff *et al*. (1974) also arrived at negative results. The authors administered rats 0.5 mg/kg LSD i.p. over 5 days and observed LSD-typical avoidance reflexes, which were not effected by tolerance development. Experiments on acute tolerance were also carried out, which proved the development of a partial tolerance (130 μg/kg i.p., per hour) within 3 h. With increasing doses, tolerance developed less often during button pushing (measurement index). The same dosage per day led to the development of tolerance after 7–8 days. By contrast, 14 days of 130 μg/kg LSD in 48-h intervals was only partially irritating to the climbing behaviour of rats (Freedman *et al*., 1964b).

Adey *et al*. (1962) investigated the effect of LSD on conditioned reflexes. They gave cats 2 × 100–200 μg/kg LSD. The reflexes, which were weakened

after the first dose of LSD, could already be triggered again fully after the second injection.

LSD led to several changes in behaviour in cats (e.g. limb flick, abortive grooming, inquisitiveness, and obvious hallucinatory behaviour), which was why some researchers used this as an animal model for the effects of LSD. An extremely high dose of 10 mg/kg LSD i.p. caused significant changes in behaviour for 4 h, whereby with an even higher dose of 50 mg/kg, the induced effects lasted for almost 8 h. Complete tolerance to a single dose of 50 mg/kg was already apparent after 1 day and lasted an astounding 5 days (Trulson *et al.*, 1977).

Cats denied LSD over a period of weeks received a single dose of 10 mg/kg LSD i.p. and then an additional test dose of 50 mg/kg [sic] after 1–24 h. The following behavioural observations (limb flick) showed the effects of tolerance. The extent of the tolerance development increased with the period between initial dose and test dose. After an hour the values were −41.1%; after 24 h they were already at −91.5%. Abortive grooming ran similar to limb flick (Trulson & Crisp, 1983).

Koella *et al.* (1964) observed the motor activity of goats in a field after a daily dose of 7.5–15 μg/kg LSD over 4 days. In this case, only a weak tolerance development could be identified. Jarvik and Chorover (1958, 1960) reported the rapid appearance of tolerance in monkeys, which lasted for 2 weeks. In their first study, they gave the animals LSD (0.01 μg/kg, i.p.) over a number of days and observed a tolerance in trained operant behaviour.

Three monkeys (*Macaca mulatta*) received LSD (1 mg/kg, i.p.) in a time interval of 6, 4, 3, and 2 days, as well as on the 4 following days. This regimen did not lead to the development of tolerance (Jonas & Downer, 1964).

In some animal experiments, no tolerance appeared in relation to the stress-related effects of LSD (Hamilton, 1960; Banerjee, 1971; Bridger *et al.*, 1973; Stoff *et al.*, 1974).

Tests on humans Isbell *et al.* (1955) carried out the first human experiments on the development of LSD tolerance using psychiatric patients (open, $n = 23$, no information on mode of application). Specific questionnaires were used as an index for mental changes. After 7 days of treatment with 30–180 μg, all test persons developed a clear tolerance. In the case of schizophrenic females, behaviour changed clearly after 100 μg LSD (open, controlled, $n = 4$). On the next day, the effect of the same dose was weaker and over the next 14 days (at the same dosage), no effect was to be seen. Through a variation of the intervals of LSD-free days, it was found out that it takes a period of 5 days to evoke the same effects. With a steady increase in the dosage (day 1:100 μg, day 2:200 μg.,

day 5: 500 µg) clear changes in behaviour were observed on the first day. On the next day only a few were ascertained and on the third and fourth days none at all. With the fifth and last dose of 500 µg LSD, practically no reactions to the substance were to be seen (Cholden *et al*., 1955).

A study on healthy subjects (open, crossover, $n = 17$) took a dosage pattern of 5–100 µg LSD over 3–6 days. Changes in perception and physiological parameters were investigated. During the time span, the effects of the LSD reduced considerably and after a few days could not be triggered at all (Abramson *et al*., 1956).

In men (former morphine addicts), it was already possible to see a significant difference in tests on behaviour and psychology as an indication of tolerance development, 3 days after chronic LSD application (crossover, double blind, 10–30 µg, 2× daily, i.v.). This difference became even clearer with a 7-day LSD administration, but was not significant in comparison to the 3-day pattern. This tolerance in relation to mental reaction was already gone 3 days after the administration of placebos (Isbell *et al*., 1956).

In a further study, LSD (open, $n = 19$, 1.5 µg/kg, p.o.) generated a high degree of tolerance after 7–10 days and after 13 days of administration, respectively (Isbell *et al*., 1961).

Hoffer (1965) was able to demonstrate tolerance towards psychological effects of LSD in healthy subjects after 2 days (crossover, double blind, $n = 14$, 100–200 µg).

The neurochemical principles behind the development of LSD tolerance have not been clarified; however, it can be assumed that particular changes within the CNS are (co-)responsible for this (Trulson & Jacobs, 1977). Buckholtz *et al*. (1985, 1988) were able to show that the chronic application of LSD leads to a down-regulation, which gives preference to 5-HT_2 receptors (without influence on the post-synaptic 5-HT_{1A} receptors). These changes go hand in hand with the development of tolerance in relation to the behavioural effect of LSD (Buckholtz *et al*., 1990).

A decrease in the intensity and duration of physiological and biochemical effects under LSD become clear in both the measurements of 5-HT metabolism in the first 60 min, and in a decrease in the rise of tryptophan and plasma corticosteroids (Freedman & Boggan, 1974; Halaris *et al*., 1975). Also of interest are long-term changes in the regulatory processes in the 5-HT and noradrenaline metabolism. These were measured 24 h after the last dose of LSD in rats, during a long-term study (14–30 days) with low doses. This showed a clear increase in noradrenaline turnover (Peters, 1974).

Peters and Tang (1977) also reported a significant reduction in the noradrenaline content in the rat cortex and a heightened tyrosine hydroxylase activity 24 h after a 14-day LSD treatment (100 µg/kg p.o.).

Cross-tolerance

A cross-tolerance appears if different substances induce a tolerance development towards one another (Table 2.13). The cross-tolerance of many hallucinogenics leads to the impression it could be due to common influence of the receptors or due to mediating processes. By contrast, there is no cross-tolerance between amphetamine and LSD (presumably due to the different places

Table 2.13 Cross-tolerance experiments with LSD and different substances

Primary substance administered	Additional substance	Species	Cross-tolerance	References
LSD	Mescaline	Humans	Complete	Balestrieri & Fontanari, 1959; Balestrieri, 1957; Wolbach *et al*., 1962a
			None	Cholden *et al*., 1955
Mescaline	LSD	Humans	Partial	Balestrieri & Fontanari, 1959; Wolbach *et al*., 1962a
LSD	Psilocybin	Humans	None	Balestrieri, 1960
			Partial	Isbell *et al*., 1961
Psilocybin	LSD	Humans	Partial	Isbell *et al*., 1961
BOL-148	LSD	Humans	Partial	Cholden *et al*., 1955; Ginzel & Mayer-Gross, 1956; Abramson *et al*., 1956, 1958 Balestrieri & Fontanari, 1959;
			None	Balestrieri & Fontanari, 1959
			Complete	Turner *et al*., 1959; Isbell *et al*., 1959b
MLD-41	LSD	Humans	Complete	Abramson *et al*., 1958
UML-491	LSD	Humans	Partial	Balestrieri, 1960
JB-336	LSD	Humans	None	Balestrieri, 1960
LSD	Amphetamine	Rats	None	Appel & Freedman, 1968; Tilson & Sparber, 1973
Amphetamine	LSD	Rats	None	Tilson & Sparber, 1973
Para-Bromo-Meth-amphetamine	LSD	Rats, rabbits	Complete	Knoll & Vizi, 1970
Ergotamine	LSD	Humans	Partial	Matussek & Halbach, 1964
LSD	THC	Humans	None	Isbell & Jasinski, 1969; Isbell *et al*., 1967
LSD	DMT	Humans	Partial	Rosenberg *et al*., 1964
		Rats	None	Mahler & Humoller, 1959

of intervention in the CNS). Anticholinergic substances also do not induce any cross-tolerance with LSD (Isbell *et al*., 1964).

Mescaline

Mescaline (3,4,5-trimethoxyphenylethylamine) is an alkaloid from the substance class of the β-phenylalkylamines, which is contained in certain types of cacti. Although mescaline is hardly related to LSD, it creates almost identical effects, so that in blind experiments, LSD and mescaline were indistinguishable. While LSD appears to intervene at the neurochemical level, above all in the serotonin metabolism, mescaline apparently affects mainly the noradrenaline metabolism.

Tests on animals Borsy *et al*. (1963) carried out experiments with LSD, BOL, UML-491, and dihydroergotamin (DHE) on the scratch reflex induced by mescaline and the hypermotility of mice. They found that LSD was particularly effective in reducing the scratch reflex. At a dose of 25 μg/kg, it brought a 42.7% reduction, and after the double dose, a 65.5% reduction. The other substances proved less effective. The central hypermotility induced by mescaline (100 mg/kg, s.c.) was stopped by previously applied LSD.

Freedman and Aghajanian (1959) carried out experiments on rats. As an index, they used the breaks taken when climbing a pole for food. After a 3- to 4-day pretreatment with LSD (130–260 μg/kg, i.p.), an administration of 10 mg/kg mescaline i.p. led to no changes. However, when the investigators administered the animals with 10 mg/kg mescaline for 10 days in a row, a dose of LSD led to similarly strong reactions as without pretreatment.

In an experiment with rats, tolerance towards 10 mg mescaline i.p. could be discerned after daily doses (7–8 days) of LSD (0.195 mg/kg, i.p.). After daily administrations of mescaline, a tolerance towards LSD could also be created (Appel & Freedman, 1968). A few years later, Winter (1971) developed a dosage scheme in which rats first received 0.2 μmol/kg LSD i.p. for 3 days, followed by mescaline at a dose of 40 μmol/kg over 2 days, resulting in the animals developing a tolerance to both substances. A renewed dosage of 0.2 μmol/kg LSD also showed no effect. Tilson and Sparber (1973) were astoundingly unable to observe any cross-tolerance in rats after 3–4 days of LSD treatment (0.045 mg/kg, i.p.) and following the administration of 3 mg/kg of mescaline. After 4–7 days of giving 3 mg/kg mescaline i.p., only a partial cross-tolerance was developed towards the administration of LSD (0.045 mg/kg).

Tests on humans Balestrieri and Fontanari (1954) investigated the cross-tolerance between LSD and mescaline on psychiatric and neurological patients. After 4–7 days of LSD administration (open, crossover, $n = 18$, 200 μg, p.o.), these

were tolerant towards a renewed dose of LSD and also towards 500 mg of mescaline. There again, only a partial cross-tolerance developed towards 200 μg LSD (11th day), after a 7- to 10-day administration of 500 mg of mescaline.

Similarly, as in the case of the animal experiments, the effects of LSD on mescaline-tolerant test persons are less restricted than mescaline effects on LSD-tolerant people (Balestrieri, 1957,1960; Balestrieri & Fontanari, 1959; Isbell *et al.*, 1961; Wolbach *et al.*, 1962a). Cholden *et al.* (1955) even postulates that LSD and mescaline do not show cross-tolerance. They treated psychiatric patients (open, controlled, $n = 4$, p.o., data on the dose are absent) for 3 days with LSD, finally applying a single dose of mescaline. No cross-tolerance was shown. Balestrieri (1957) gave psychiatric and neurological patients LSD (open, $n = 13$, 200–250 μg, p.o.) for 3–5 days. A dose of mescaline (no dose given) taken later showed no effect in comparison to controls (without pre-treatment with LSD).

In a detailed investigation by Wolbach *et al.* (1962a), former opiate addicts were treated with 1.5 μg/kg LSD i.m. or 5 mg/kg mescaline i.m. (single blind, crossover, $n = 10$) for 14 days. The developed tolerance did not concern heart frequency and body temperature changes. After these preliminary treatments, the patients were exposed to a test dose (not of the primary substance used). The result was that 5 mg/kg of mescaline was tolerated by people with LSD toleration. In the reverse case, 1.5 μg/kg LSD i.m. also led to tolerance in the other test group; however, body temperature, heart frequency, and patellar tendon reflex were excluded.

Psilocybin

Psilocybin (*O*-phosphoryl-4-hydroxy-*N*-dimethyltryptamin) is the phosphorous acid ester of psilocins and is to be found in diverse species of mushrooms (psilocybe, stropharia, conocybe a.o.).

Wolbach *et al.* (1962b) treated patients (former opiate addicts) with 37.5–75 μg/kg psilocin in addition to 75–150 μg/kg psilocybin i.m. (simple blind, cross-over, $n = 10$). One microgram per kilogram (μg/kg) LSD is equivalent to about 45 μg/kg psilocin, or about 30 μg/kg psilocybin.

Psilocybin is chemically more closely related to LSD than to mescaline. Psilocybin and LSD are cross-tolerant to each other; it remained controversial however, whether the LSD reaction with psilocybin tolerance is stronger (Abramson *et al.*, 1960) or weaker than by LSD tolerance (Isbell, 1956).

Tests on animals Appel and Freedman (1968) were able to show in rats that dosing psilocybin (1.5 mg/kg, i.p.) over 10 days, as opposed to LSD (0.195 mg/kg, i.p.), created the same tolerance as a pretreatment with LSD.

Conversely, the animals also become tolerant towards psilocybin when given a daily dose of LSD.

Tests on humans Isbell (1959) investigated the effects of psilocybin (57–114 μg/kg) in comparison to LSD (1.0–1.5 μg/kg) on healthy humans (simple blind, crossover, $n = 9$, p.o.). According to the authors, both substances created small-grade increases in the body temperature, heart and breathing frequency, as well as in the systolic blood pressure. The threshold for the triggering of reflex actions is lowered. After both substances, fear, disruption of thought, and changes in perception are reported to have appeared. The effects of psilocybin lasted for a shorter duration and a 100–150 times dose was necessary to invoke similar effects of LSD.

Balestrieri (1960) treated patients with 200 μg LSD p.o. for 5–8 days (open, controlled, $n = 5$). The subsequent administration of psilocybin (6 mg i.m.) triggered equally strong reactions as to those in the test group, meaning it can lead to tolerance development.

In experiments with healthy humans (open, crossover, $n = 19$), who had developed tolerance to either psilocybin (210 μg/kg, p.o.) or LSD (1.5 μg/kg, p.o.) within different periods of time, cross-tolerance with single doses of 210 μg/kg psilocybin or 1.5 μg/kg LSD appeared in almost half of the cases. Parameters, in which no tolerance was shown, were blood pressure, the patellar reflex, and heart frequency in those tolerant to LSD, and body temperature in those tolerant to psilocybin (Isbell *et al.*, 1961).

BOL-148

The bromine derivative of LSD (BOL-148) is just as potent as LSD in regard to the antagonization of serotonin-induced contractions in isolated dissections of smooth muscle cells. However, it possesses no hallucinogenic effects (Cerletti & Rothlin, 1955). Accordingly, serotonin antagonism does not appear to directly correlate with the psychopharmacological effects of some lysergic acid derivatives. BOL-148 and LSD develop cross-tolerance, if one takes the different dosage of both substances into account.

Tests on animals Appel and Freedman (1968) examined rats that were pretreated with BOL-148 (1.3 mg/kg, i.p.) for 7–8 days. A single dose of 0.13 mg/kg LSD i.p. applied afterwards was only able to trigger the known effects in a limited way. Conditioned button pressing to obtain food served as the parameter for the measurement of possible changes through the influence of both lysergic acid derivatives. Furthermore, after daily administration of 0.195 mg/kg LSD i.p. for 1 week, a partial cross-tolerance was able to be demonstrated with a subsequent administration of BOL-148 (1.3 mg/kg, i.p.). Under identical

experimental conditions, a partial cross-tolerance also appeared after psilocybin (1.5 mg/kg, i.p.) in cases of BOL-148 tolerance.

Tests on humans Balestrieri and Fontanari (1954) administered neuropsychiatric patients 2.5 mg BOL-148 for 4–8 days. A tolerance towards BOL-148 itself did not appear. LSD (open, crossover, $n = 18$, 200 μg, p.o.) administered afterwards, however, was considerably weakened in its effect.

Cholden *et al.* (1955) also reported a cross-tolerance between LSD and LAE-321 or BOL-148 (open, controlled, $n = 4$, psychiatric patients, no dosages given).

An LSD tolerance (no information on experimental design, $n = 6$, 50–75 μg, p.o.) was reported by Ginzel and Mayer-Gross (1956), after only 1–2 days of low-level BOL-148 (2–3 mg, p.o.) administration. In contrast to this, an i.v. injection of 0.5–1.0 mg BOL-148 during the maximum of LSD effect did not lead to a restricting effect in four test persons. Abramson *et al.* (1956) treated healthy humans twice daily with a dose of 100 mg BOL-148 for 2 days (open, crossover, $n = 17$, p.o.). A partial cross-tolerance appeared towards a follow-up dose of LSD (25 μg). It has to be taken into account here that a very small LSD dose was chosen.

Abramson *et al.* (1958) examined five test subjects for the effects of LSD (double blind, crossover, 50–100 μg, p.o.) after a 5- to 6-day pretreatment with 1 mg BOL-148. The authors were able to prove a partial cross-tolerance.

In experiments by Balestrieri and Fontanari (1959), the effects of LSD (open, crossover, $n = 18$, 200 μg, p.o.) on neurological patients (e.g. epilepsy, polyneuritis, and neurosyphilis) were not antagonized, following 4–8 days of an increasing dose of BOL-148 (up to 2.5 mg/d, p.o.).

Isbell *et al.* (1959b) found cross-tolerance between BOL-148 and LSD (double blind, crossover, p.o.) in former opiate addicts ($n = 33$), using vital parameters and questionnaires. They then administered 3 mg BOL-148 for 5 days and afterwards 1 μg/kg LSD. With a prolonged administration of BOL-148 (3–4 weeks) in high doses (30 mg/day, p.o.) it might be possible to create a complete resistance to LSD (open, $n = 6$, 150–200 μg, p.o.). This was described in the case of chronic schizophrenic patients by means of the subjective description of the degree of agitation, fear, and hallucinations (Turner *et al.*, 1959).

Other lysergic acid and amphetamine derivatives

Amphetamine (α-methylphenethylamine) and its derivatives are a group of synthetically produced substances, whose parent substance is phenylethylamine.

Tests on animals Appel and Freedman (1968) applied LSD (0.195 mg/kg, i.p.) to rats for 7–8 days. A subsequent injection of amphetamine (1–2 mg/kg, i.p.)

led to the same changes in conditioned reflexes as without pretreatment with LSD. In addition, Tilson and Sparber (1973) were unable prove a cross-tolerance between LSD and amphetamine in rats. They were given 0.015 mg/kg LSD i.p. over 4–6 days and finally 0.15 mg/kg of amphetamine. When carried out in the reversed order, the experiment led to the same result, except that amphetamine even for 6–9 days caused no cross-tolerance towards LSD.

Knoll and Vizi (1970) investigated the effect of para-bromo-methamphetamine (V-111) and LSD on the avoidance and escape behaviour of rats in a modified jump test, as well as hyperthermia in rabbits. A pretreatment with 10 mg/kg V-111 over a time period of 3 weeks on rats led not only to tolerance, but also to cross-tolerance after the administration of LSD (0.5–2.0 mg/kg). Rabbits were given a dose of 10–100 mg/kg V-111 for 3–40 days. After this period, LSD dosed at 50 mg/kg was unable to induce hyperthermia in the animals, because a cross-tolerance had developed.

Tests on humans In normal test subjects, cross-tolerance developed with increasing doses of MLD-41 (double blind, crossover, $n = 5$, 100–350 μg, p.o. over 5 days) with respect to 100 μg LSD (Abramson *et al.*, 1958). With neurological patients (e.g. polyneuritis and multiple sclerosis), who received UML-491 (open controlled, n = 5, 2–4 mg, p.o) for 5–6 days, a dose of 200 μg LSD invoked only a modest reaction in comparison to controls. However, when this patient-collective was given 150 μg of LSD an hour after UML-491 (3 mg, p.o.), the LSD influence remained unaffected (Balestrieri, 1960). A cross-tolerance towards 10 mg of the synthetic, anti-cholinergic functioning hallucinate, tropane ester JB-336 (N-methyl-3-piperidyl benzilate) could not be observed on neurological patients after 5–8 days of pretreatment with LSD (open, controlled, $n = 4$, 200 μg, p.o.) (Balestrieri, 1960).

Ergotamine

It is known from animal experiments that hydrated ergoline alkaloids working sympatholytically block central vegetative LSD effects (Rothlin *et al.*, 1956). There are, however, hardly any investigations into the effect of sympatholytics on the effect of LSD in humans. Imitating animal experiments, Matussek and Halbach (1964) investigated the effect of ergotamine on the LSD effects in humans. Seven healthy test persons received 2–4 mg ergotamine p.o., for 3–5 days and then 2 mg ergotamine combined with LSD (open, crossover, $n = 7$, 1.5 μg/kg, p.o.), as well as a renewed dose of ergotamine after 4 h. The first series of experiments showed that the psychological effects of LSD are increased by ergotamine and last on average 3–5 h longer. By contrast, mydriasis was inhibited and pulse frequency lowered. Blood pressure showed no differences.

Tetrahydrocannabinol (THC)

Δ^9-Tetrahydrocannabinol belongs to the cannabinoids, which is synthesized from the hanf plant, *Cannabis sativa*, and is mainly responsible for the psychotropic effects of this plant. It is a relatively lipophilic, nitrogen-free, phenolic compound, with a 21 carbon nucleus (Kleiber & Kovar, 1998).

Tests on animals Silva *et al*. (1968) trained rats to obtain water via a push of a button. Afterwards, the animals were given a daily dose of LSD (130 μg/kg, i.p.) for 3 days, which led to development of tolerance. However, the effect of THC (130 μg/kg, i.p.) remained uninfluenced. In the reverse of the experiment, after 2–4 weeks of daily THC administration (10 mg/kg, i.p.), a tolerance towards THC did result; however, a cross-tolerance towards LSD did not (200 μg/kg, i.p.).

Tests on humans Isbell and Jasinski (1969) compared objective and subjective effects of 0.5–1.5 μg/kg LSD (double blind, crossover, $n = 8$, i.m.) with those from 75 and 225 μg/kg THC (per inhalation) on former opiate addicts. The effects, which could be taken objectively, were clearly different between LSD and THC. The rise in body temperature and systolic pressure, mydriasis, as well as a lower threshold for reflexes, could only be found with LSD and not THC. However, THC created a clearer tachycardia than did LSD. Subjective effects of both substances could not be differentiated with the methods used here (questionnaires by Abramson, 1956 and Haertzen, 1966). During the investigation of cross-tolerances, the same patient-collective ($n = 10$) were given 0.5–1.5 μg/kg LSD on 11 consecutive days. On the twelfth day, the application of THC (250 μg/kg, per inhalation) resulted in no cross-tolerance.

Isbell *et al*. (1967) carried out tests using LSD and THC. After repeated injections of 1.5 μg/kg LSD i.m. (number of injections not given), a tolerance towards LSD appeared, but none towards 250 μg/kg THC (per inhalation).

Tryptamine

Tryptamine (β-Indolyl-3-ethylamin) is a biogenic amine produced by splitting a carboxylgroup from the amino acid tryptophan. It stimulates the contraction of smooth muscle. The tryptamin derivative, *N*,*N*-dimethyltryptamin (DMT) causes similar subjective effects as LSD. Therefore, 0.5 mg/kg of DMT is the equivalent of a dose of 1.5 μg/kg LSD (Rosenberg *et al*., 1964).

Tests on animals Cross-tolerance between LSD and DMT could not be found after repeated injections of LSD (0.3–0.7 mg/kg, i.p.) and DMT (8–27 mg/kg) in rats (Mahler & Humoller, 1959). Cross-tolerance was also not found in EEG examinations on cats with DMT (Gillin *et al*., 1973) and with 5-MeO-DMT in neuroendocrinological studies on rats (Simonovic & Meltzer, 1979).

It must be pointed out that DMT does not invoke complete tolerance development, even in relation to behavioural changes in monkeys and also in strict dose regimes (every 2 h for 21 days) (Cole & Pieper, 1973; Kovacic & Domino, 1976).

Tests on humans Even a complete tolerance to LSD (simple blind, crossover, $n = 5$, 14 days, in increasing doses up to 1.5 μg/kg i.m. per day) presents no cross-tolerance with a hallucinatory dose of DMT (1 mg/kg). A follow-on increase in dosage to 3 μg/kg LSD (twice daily up to the 37th day) only showed small signs of cross-tolerance. Physiological measurements brought no signs of tolerance, while clear references as to such were found in questionnaires and clinical observations (Rosenberg *et al.*, 1964).

In humans, a twice daily dose of DMT (open, controlled, $n = 4$, 0.7 mg/kg, i.m.) for 5 days brought forth no development of tolerance to LSD (Gillin *et al.*, 1976). In another study on humans, there were no indications regarding the development of tolerance seen in psychological effects after four injections of DMT (double blind, crossover, $n = 12$, 0.04–0.4 mg/kg, i.v.; Strassman *et al.*, 1994), given in 30-minute intervals.

Chapter 3

Interactions of LSD

Interaction with endogenous substances

Serotonin

When comparing the structural formulas of lysergic acid and serotonin (5-hydroxytryptamin), one can recognize the structure of tryptamine in both compounds. Serotonin is stored in cell vesicals and emptied from them. It is broken down by the enzyme monoamine oxidase. Serotonin is unable to pass the blood–brain barrier. Serotonin is to be found in the periphery of the body (above all, gastrointestinal tract and blood cells), as well as being a transmitter in the CNS. There it occurs in pre-synaptical terminals of synapses. The cell bodies of the neurons that form serotonin almost all lie in a particular area of the nine raphe nuclei in the pons and in the upper brainstem. From here, axons lead off into various parts of the CNS and the spinal fluid. Serotonin released from the pre-synaptic terminals mostly works to inhibit the function of the post-synaptic cells (Wellhöner, 1997).

After the isolation and identification of serotonin, the interest in its role as a neurotransmitter was heightened due to the apparent interaction between LSD and the serotonin system. Twarog and Page (1953) were the first to discover the presence of serotonin in brain extracts, and Gaddum reported (1953) that LSD antagonized the effect of serotonin in periphery tissue. In the following year, Gaddum and Hameed (1954), as well as Woolley and Shaw (1954a,b), supposed that the strong psychoactive potency of LSD came from a blockade of serotonergic receptors in the CNS. Further authors were able to prove the anti-serotonergic activities of LSD (e.g. Gaddum *et al.*, 1955; Costa, 1956).

If rats are killed and examined 10, 20, and 120 min after receiving LSD (130 and 260 μg/kg), a rise in the serotonin concentration in the brain of about 17–24% can be observed (Table 3.1). Here the minimal effective dose correlates (visible changes) with the threshold dose for measurable changes in the brain concentration of biogenic amines. A dose of 520–1300 μg/kg LSD does not significantly differ in quality (with the exception of longer effectiveness) to 130 or 260 μg/kg (Freedman, 1963). King *et al.* (1974) also observed a rise in the serotonin concentration in the brains of rats after LSD administration (25 μg/kg, i.v.).

Table 3.1 Effects of LSD on brain amines

	Number of subjects	µg/g	Δ %
Serotonin			
Reserpine (1, 2, 4 mg/kg)	52	83	
R + LSD (130, 520, 1300 µg/kg)	77	190	+ 117%
Controls	50	365	
LSD (130 µg/kg)	43	450	+ 24%
Controls*	132	525	
LSD (520–1300 µg/kg)*	175	628	+ 17%
Noradrenaline			
Controls	8	560	
LSD (1300 µg/kg)	18	442	– 21%

(*Fluorimetric method, cf. Freedman, 1963, S. 844)

Tests on animals Gaddum (1953) carried out tests on isolated rat uteruses and discovered that a concentration of 0.6 µg/l LSD reduced the serotonin-induced muscle contraction (15 µg/l) so that after 10 min the serotonin dose had to be doubled to achieve the original result. LSD (100–300 µg) inhibited the effect of 100–200 µg serotonin in the vasoconstriction of pulmonary vessels in cats. On dogs' vessels, LSD (100 µg) completely inhibited the effect of 30–250 µg serotonin. On the vessels in the isolated ears of hares, the inhibiting effect of LSD on the effect of serotonin could not be clearly shown, because LSD itself showed vasoconstrictive properties (Ginzel & Kottegoda, 1953).

Gaddum *et al.* (1955) investigated the ratio of the equiactive dose of serotonin, before and after LSD. On isolated rats' uteruses, 3 min after LSD (10 µg/l), the ratio was 20/10, meaning that 20 ng serotonin creates the same effect as 10 ng before LSD application. After 15 min the proportion was 50/4 (72 min: 200/7, 88 min: 300/6, 104 min: 350/6).

5-Hydroxytryptophan (5-HTP)

Tests on animals 5-Hydroxytroptophan is a non-proteinogenic amino acid and an intermediate in the synthesis of serotonin from tryptophan.

The conversion of tryptophan via 5-HTP to serotonin in rats is slowed by LSD administration for about 2 h (Lin *et al.*, 1969). Since no indications were found of a direct interaction with enzymes, an indirect feedback mechanism or LSD-induced inhibition of raphe nuclei activity has been postulated (Freedman & Halaris, 1978).

Siva Sankar *et al*. (1962a, 1962b) administered LSD (500 µg, i.v.) and [^{14}C]-5-HTP (0.92 mg, i.v.) alone or together to rabbits. The total renal radioactivity changed considerably following the LSD administration. The total radioactivity changed only slightly in other tissues such as liver, spleen, and lung. In general, the authors determined a rise in the metabolism of serotonin and increased serotonin levels in all parts of the body after administration of LSD (with exception of the cerebrum).

Tests on humans Brengelmann *et al*. (1958) treated subjects with 5-HTP to raise the serotonin concentration in the brain. According to these authors, 5-HTP lowered the effects of the LSD (double blind, crossover, $n = 5$, 60 µg LSD, i.v.).

Pare and LaBrosse (1963) gave 5-HTP to 13 subjects (double blind, crossover, $n = 13$, 25–60 mg, i.v.), followed an hour later by LSD (30–60 µg, i.v.). The average values of the symptoms rating scale showed fewer symptoms when LSD was combined with 5-HTP.

Klee *et al*. (1960) gave their test subjects LSD following a 20 min i.v. infusion of 5-HTP (1.11 mg/min). They found no influence on the effects of the LSD.

Pare and LaBrosse (1963) investigated the interaction between LSD and 5-HTP in healthy subjects. The authors gave 5-HTP (double blind, randomized, crossover, $n = 13$, 25–60 mg, i.v.) or a placebo followed after 1 h by LSD (30–60 µg, i.v.). The average values of the symptoms rating scale showed fewer symptoms when LSD was combined with 5-HTP, but the results were statistically significant for only 30 min after LSD. The results of the Clyde mood scale changed on administration of LSD and placebo, but after pre-treatment with 5-HTP the values did not change. These results strengthen the hypothesis that pretreatment with 5-HTP leads to a slight reduction of LSD symptoms. The authors postulate a rise of brain serotonin concentration by the precursor substance 5-HTP as the cause of that reduction.

Vojtechovsky *et al*. (1967) investigated the interaction between 5-HTP (100 mg, p.o.), tryptophan (10 g, p.o.), and LSD (open, controlled, $n = 13$, 200 µg, p.o.) on former alcohol-dependant patients. 5-HTP strengthens the effect of LSD, above all in the areas of visual and acoustic perception. When tryptophan is combined with LSD, symptoms similar to alcohol intake are triggered, with a feeling of drunkenness, tremors, and thought blockages. The phenomena of derealization or illusion did not occur; instead, there were two cases of seriously prolonged LSD-induced psychoses. Objective methods of measurement (questionnaires after Abramson *et al*. (1955a), Clyde Mood Scale, vital parameter) confirm that central LSD effects are increased and peripheral effects are diminished.

Biogenic amines

During the 1950s and 1960s, many hypotheses assumed that LSD provoked an outpouring of catecholamines. The relevant tests, however, brought no uniform results. Pieri *et al*. (1978) showed a dose- and time-dependent reduction in homovanillic acid (HVA) in rats' brains after LSD administration. Keller *et al*. (1978) observed a slight increase in HVA after 100 μg/kg LSD, and after 1000 μg/kg, a clear increase in the striatal, limbic, and cortical regions of the rat brains.

Palmer and Burks (1971) showed that LSD effectively reduces the effect of c-AMP on noradrenaline in the hypothalamus and brainstems of rats. LSD does not change the basal level of c-AMP; however, it reduces the α-adrenoreceptor-mediated noradrenaline reaction by about 25%.

The only direct measurement of the dopamine output (from the perfunded head of the nucleus caudatus of the rat) showed dopamine depression for 3 h after LSD administration (DaPrada *et al*., 1975).

Hoagland *et al*. (1955) was the first to suspect an interaction with the adrenaline metabolism as a potential mechanism of the effect of LSD. On this, the following proofs can be pointed out:

- LSD influences the adrenaline level in serum in several ways. Liddell and Weil-Malherbe (1953) treated 13 psychiatric patients with LSD (40 μg, i.v. or 60 μg, p.o.). After the initial increase in the adrenaline level in the plasma, a drop occurred after 1 h, and after 2 h a renewed increase occurred. Studies by Hoffer and Osmond (1960) supported this.
- LSD activates the adrenal gland in animal experiments. The adrenal medulla increases its activity, as can be gauged from the increased intake of radioactive phosphor. The adrenal cortex is also activated by LSD. Sackler *et al*. (1963) observed an increased 17-ketosteroid secretion after LSD administration (50 or 75 μg, i.p.). Ganong *et al*. (1961) investigated the effect of LSD (50 μg/kg, i.v.) on the adrenal cortex in dogs. LSD brought on a light increase in 17-hydroxycorticoid secretion. Adrenalin and noradrenaline values before and after LSD administration did not significantly vary.
- When determining the ascorbic acid concentration in the adrenal glands of rats, Costa and Zetler (1958b) noticed that LSD (10 μg/kg, i.p.) in combination with adrenaline (25 μg/kg, i.p.) produced a stronger reduction of the adrenal ascorbic acid content, than after adrenaline administration alone.
- A study with psychiatric patients showed an initial increase in the plasma adrenaline when they were given LSD (open, crossover, 40–60 μg, i.v.),

followed by a drop to below the initial levels and a renewed increase after a number of hours (Manger *et al.* 1956). Rinkel *et al.* (1955) gave schizophrenic patients noradrenaline, or adrenaline (each 0.025 cc, i.v.) before and 2 h after LSD (open, controlled, $n = 15$, 0.5 µg/kg, p.o.). The noradrenaline-induced increase in blood pressure was not significantly changed by LSD. LSD significantly reduced the blood pressure increase caused by adrenaline, when the adrenaline was administered 2 h after the LSD.

– Data from psychiatric patients who were given LSD (open, crossover, $n = 14$, 150–300 µg, p.o.), pointed to a constant increase in the adrenaline level with variable noradrenaline rates (Elmadjian *et al.*, 1958). In 24-h collected urine from seven healthy subjects, Messiha & Grof, 1973 found a clear reduction in the excreted levels of dopamine and serotonin after LSD administration (open, crossover, $n = 7$, 200–300 µg, p.o.). The noradrenaline, HVA, vanillylmandelic acid and 5-HIAA levels did not change.

However, there is also proof for an irrelevance of the interactions of LSD with the katecholaminergic systems:

– Regarding the vasoconstriction of pulmonal vessels in cats, LSD (100–300 µg) only had a limited influence on the effects of adrenaline and noradrenaline. The reaction of the vessels in the back legs of dogs to 1 µg adrenaline was only slightly weakened by LSD (100 µg) (Ginzel & Kottegoda, 1953). Graham and Khalidi (1954) proved LSD had a restricting effect on the stimulation of dissected smooth muscle and isolated rabbits' hearts by adrenaline and noradrenaline.

– Costa and Zetler (1958a) tested the threshold dose of diverse substances for the stimulation of nicotinergic membranes (cats) after i.v. injections of adrenaline. Thereby the threshold dose for an increase in the adrenaline effect is lowest with LSD.

– A study by Liddell and Weil-Malherbe (1953) reported plasma concentrations of adrenaline and noradrenaline remaining the same after LSD (open, n = 13, 50 µg, p.o.).

– Hollister (1964b) and Hollister and Moore (1967) investigated the effect of LSD (open, crossover, $n = 13$, 2 µg/kg, s.c.) on the excretion of catecholamines in healthy subjects. According to this, LSD caused no significant changes in the catecholamine excretion.

The concentration of dopamine metabolites 3,4-dihydroxyphenylacetate (DOPAC) in the striatum of rat brains was reduced by less than 1 mg/kg LSD, while higher doses (10 mg/kg) caused a rise in the first hours after application. In contrast to this, Persson (1977a) found an increase in striatal DOPAC

concentrations along the whole dose range of LSD (50 µg/kg to 4 mg/kg). At lower LSD doses (50 µg/kg), the 3-methoxytryptamine concentration sank, while a 10 times higher dose raised the concentration.

Cates *et al*. (1962) investigated the effect of LSD on the histamine concentrations in the liver, lungs, kidneys, spleens, hearts, and brains of rabbits. LSD (500 µg, i.v.) caused a reduction in the histamine concentration, above all in the brain and heart muscle, as well as an increase in the spleen. The authors suspected that LSD restricted the release by histamine reservoirs.

Broer *et al*. (1963) injected rabbits with radioactive amines (5-HTP, histidine, noradrenaline, serotonin, histamine) and LSD (150–175 µg/kg). LSD increased tissue concentration of radioactivity in all organs except the liver, lungs, and spleen with 5-HTP. The same was the case for histidine, with a clear increase in the whole body (with the exception of the kidney). Particularly small concentrations were found in the brain, the highest content being in the liver and spleen. Noradrenaline was to be found mainly in the heart (lowest value: cerebellum). LSD increased the serotonin level in all tissue (excepting the cerebrum), whilst the levels of histamine and noradrenaline decreased after injections of 5-HTP. In this context, the theory was put forward that LSD supports the metabolism via the binding of serotonin and the setting free of noradrenaline (Siva Sankar *et al*., 1964). There may have been sufficient proof brought forward that LSD influenced the concentration of biogenic amines, in particular that of serotonin; however, there are only a few sensible conclusions to be drawn from the gathered data. For example, the bromine derivative of LSD (BOL-148) possesses a comparable anti-serotonergic potency to LSD without any psychological effects. This can be interpreted as an indication that the anti-serotonergic activity does not play a key role in the effects of LSD.

With reference to the changing of catecholamine by LSD in the human organism, it has to be noted critically that the prevailing conditions and expectations have a very strong influence on the individual course of the psychophysical reactions towards LSD. Consequently, conditions of euphoria as well as fear have to be reckoned with, depending on the basic conditions, psychological disposition, and expectations. As is known, fear and euphoria, in particular, massively influence the catecholamine plasma level. Therefore, it should not be assumed that a monocausal origin is behind these kinds of changes.

Interactions with exogenous substances

LSD is the best researched hallucinogenic compound drug. This is also the case in relation to the interaction with other substances. Clinical studies focus

primarily on the interaction of LSD with neuroleptics. This is done with the thought in mind that due to their anti-psychotic activity, they could influence or suppress the effects of LSD. In the end, almost all kinds of psychopharmacological substances (known up until 1970) had been tested for their interaction with LSD. These studies were carried out on, amongst others, spiders, fish, monkeys, and humans (Elder, 1965). The large range and variability of the tests and methods used for the identification of LSD-induced symptoms makes a systematic description difficult (Wyatt *et al.*, 1976).

It has to be mentioned that following a long period of inactivity (cf. Claridge, 1978) a large number of non-published drug-discrimination studies were conducted during the 1980s. Hundreds of potential neuroleptic compounds were tested on animals in an attempt to antagonize LSD discrimination. This eventually lead to the development of some major 'second generation' neuroleptics such as risperidone (see Colpaert, 2003 for review).

Colpaert, F. C. (2003) Discovering risperidone: the LSD model of psychopathology. Nature Reviews Drug Discovery 2, 315-320.

Psychiatric drugs

Chlorpromazine

The substance most often used for the treatment of 'bad trips', referring to scary and uncomfortable psychological reactions experienced with LSD, was chlorpromazine. It was experimented with before, during, and after the administration of the hallucinogenic.

In pretreatment with chlorpromazine, doses of between 0.35 and 9 mg/kg were given, from 30 min up to a number of days before LSD administration p.o. As can be found in numerous publications, chlorpromazine proved itself to be a quasi-complete antagonist for the effects of LSD (Cholden *et al.*, 1955; Cooper, 1955; Giberti & Gregoretti, 1955; Schwarz *et al.*, 1955; Hoch, 1956b; Isbell, 1956; Mac Donald & Galvin, 1956; Isbell & Logan, 1957; Sandison & Whitelaw, 1957).

Tests on animals Cook and Weidley (1957) trained rats ('condition avoidance escape response'). Doses of 1.5 mg/kg LSD s.c. blocked this reflex significantly. Higher doses also affected the reaction towards unconditioned stimuli such as electric shocks. It apparently concerns a specific blockade, because other motoric abilities of the animals remain uninfluenced. Chlorpromazine achieves a specific blockade with 5 mg/kg and does not inhibit conditioned reflexes, even at a dose of 40 mg/kg. These effects were significantly antagonized by 0.1–0.5 mg/kg of LSD.

As much as 5 mg/kg chlorpromazine i.v. or i.m. also worked on cats, antagonizing LSD symptoms when LSD (400 µg/kg i.v.) was injected daily for 3 days. A triple dose of chlorpromazine had the same effect as 5 mg/kg on the effect of LSD (Elder *et al*., 1957).

Appel and Freedman (1964) trained rats to press a button to obtain food. This ability was strongly inhibited with the administration of high doses of LSD (crossover, 130 µg/kg i.v.). An administration of chlorpromazine (30 µg/kg i.v.), 1 h before LSD was given, led to a clear improvement in this inhibition. Ray and Marrazzi (1961) achieved similar results with the same dose of chlorpromazine studying the drinking behaviour of rats. Dixon (1968) observed the influence of two phenothiazines, chlorpromazine and perphenazine, on LSD-induced behavioural changes in rats. After chlorpromazine (1–10 mg/kg s.c.) or perphenazine (0.3–3.0 mg/kg s.c.), LSD (double blind, controlled, $n = 12$ per substance, 3–5 mg/kg, s.c.) was administered. Both substances reduced the LSD-typical behaviour, as well as the increase in motoric activity. Perphenazine only affected these indices partially, whilst chlorpromazine exhibited a fully antagonistic effect.

Chlorpromazine (0.3 and 1.5 mg/kg) strongly inhibited the LSD-induced hyperthermia in rabbits (10 µg/kg, i.v.) (Eichenberger & Friolet, 1957).

In experiments with pigeons, in which LSD induces hypothermia (in contrast to most mammals), Hoffman (1958) tested the effect of LSD (open, crossover, 1 mg/cc, s.c.) in combination with chlorpromazine. At a dose of 10 mg/cc, chlorpromazine inhibited LSD-induced hypothermia.

Konzett (1956) tested the antagonism between LSD (0.15 mg/kg, s.c.) and chlorpromazine using the LSD-induced blood sugar increase in rabbits. The phenothiazine derivative reduced LSD-induced hyperglycaemia at a dose of 10 mg/kg.

Because chlorpromazine did not work on the peripheral sugar mobilizing effects of s.c. injected adrenaline, the author presumed a central effect of antagonism.

Djahanguiri and Giuti (1966) injected 10 dogs with LSD (1 µg/kg) and 2 mg/kg chlorpromazine simultaneously. In contrast to the administration of LSD alone, no significant modifications in the EEG occurred. However, an hour after the injection, a clear increase in the total indices of the Δ-, θ-, and α-rhythm could be seen.

It is remarkable that conflicting results were also reported in animal experiments. Halasz *et al*. (1969) studied the effect of different dosages of chlorpromazine in combination with LSD on the conditioned behaviour of monkeys and cats. In cats, chlorpromazine (200 µg/kg, i.p.) protected against the usual LSD-induced changes in behaviour. A dose of 300 µg/kg chlorpromazine left the conditioned behaviour of the animal subjects uninfluenced, but after

a combination with LSD (10 μg/kg, i.p.) a strengthening of the LSD effect occurred. The changes in behaviour clearly surpassed the extent of a single LSD dose alone. This effect was also observed in rats. After 0.15 mg/kg (i.p.) chlorpromazine in combination with LSD (open, 10 μg/kg i.p.), the conditioned behaviour of the animals was fully visible again, although it had previously disappeared under the effect of LSD. A dose of 1.0 mg/kg of chlorpromazine multiplies the effect of the LSD on this behaviour.

Tests on humans In low doses (0.35 mg/kg), chlorpromazine increases the threshold dose for LSD (double blind, crossover, $n = 18$, 15 μg p.o.), which is necessary to trigger pupil dilatation in test subjects, if it is administered shortly before LSD (Murphree, 1962). Regarding pretreatment using higher doses (0.7 mg/kg) over a period of many days, the subjects primarily showed a reduction in LSD-induced psychomotoric activities (Abramson, 1956), reduced fear and heightened mood, and a delayed beginning of effect and a shortened period of effectiveness (Giberti & Gregoretti, 1955).

The latter authors gave neurotic patients 3–9 mg/kg of chlorpromazine for a few days before LSD was given (open, $n = 5$, 60–150 μg p.o.). The LSD experience was described by the test subjects as being subjectively more tolerable, although changes in perception, memory, and orientation occurred in the same manner as without chlorpromazine. Abramson (1956) showed that p.o. applied chlorpromazine, in contrast to i.v.-administered chlorpromazine, did not invoke an inhibition of LSD symptoms; rather, it increased them. In this experiment regime, the test persons received either chlorpromazine (0.7 mg/kg) 2 h before LSD (double blind, crossover, $n = 3$, 25–50 μg p.o.), at the same time as LSD, or 2 h after LSD. Isbell and Logan (1957) conducted experiments on non-psychotic, former morphine addicts. Doses of 50–100 mg chlorpromazine were used; those taking part afterwards being given LSD (double blind, randomized, crossover, $n = 39$, 40–60 μg, p.o.). Above all, the group ($n = 19$) who were given 75 mg chlorpromazine, and 30 min later 60 μg LSD, showed a clear reduction in mental effects compared to the placebo application. Furthermore, a lesser pupil dilatation was observed. Blood pressure and questionnaire instruments according to Jarvik *et al.* (1955a) only showed a trend in the direction of inhibition.

Schwarz *et al.* (1955) injected test subjects with 25 mg of chlorpromazine i.m. to reduce the effect of an LSD administration (open, $n = 11$, 50 μg, p.o.). The visible minimal EEG changes (suppression of the α-rhythm) due to LSD, seen before the administration of the neuroleptic, disappeared after the injection with chlorpromazine.

Hoch (1955) carried out experiments on test persons with chlorpromazine in combination with LSD. Here, chlorpromazine (25 or 60 mg, i.v., no other

information on test subjects and test design) was administered during the maximum of effect (approximately 1 h after LSD application). After 3–7 min, typical LSD effects were eliminated, such as hallucinations, depersonalization, delusions, and fear and excitement; vegetative changes were also weakened. After 5–20 min, the effect of the chlorpromazine slackened and the LSD effects reappeared.

In the experiment by Isbell and Logan (1957) described earlier, chlorpromazine (75 mg, p.o.) was also given to 12 subjects, 1.5 h after 60 μg of LSD. This reduced the LSD-induced mydriasis; psychological effects were not influenced. The application of 25 mg chlorpromazine i.m. 1.5 h after different doses of LSD (double blind, randomized, crossover, $n = 24$, 60–150 μg, p.o.) led to a significant reduction of pupil dilation and psychological effects.

Clark and Bliss (1957) arrived at different results. In their experiments, 50 mg chlorpromazine were administered 1.5 h before LSD (double blind, crossover, $n = 6$, 0.5–1.0 μg/kg, p.o.) The authors were unable to recognize any significant influence on the somatic and psychological effect of the LSD through the effects of the chlorpromazine.

Schwarz *et al*. (1967) documented two cases of paradoxical reactions to chlorpromazine when given to suppress the effects of LSD.

Other neuroleptics

Tests on animals Dimenhydrinate (5 mg/kg, i.v.) caused similar symptoms in cats to reserpine, when it was given shortly before 400 μg/kg LSD. Long-lasting catatonic-like states were described with combinations of both. However, promazine displayed no interaction with LSD with the same dosage in cats (Elder *et al*., 1957).

Appel and Freedman (1964) trained rats to press a button if they wanted food. A pretreatment with 4 mg of tetrabenazine (inhibition of the dopamine and noradrenaline storage in the CNS), 5 h before, significantly strengthened the reaction of the animals to LSD (crossover, $n = 6$, 40 μg/kg, i.v.). Given singly, both substances worked to inhibit the learned reflex. In further experiments, rats were treated with tetrabenazine 10, 15, and 24 h before LSD administration. In these cases, no changes were observed in the reactions to LSD. In the experiments, it was proved that no degradation of the amine occurred; however, an influence on the effects of LSD was also not found.

A pretreatment using 15 mg/kg benzquinamide (first used as an anxiolytic psychotropicum, later as 'post-opioid-breathing analepticum' and antiemeticum), apparently increased the inhibiting effect of LSD (crossover, $n = 6$, 40 μg/kg, i.v); however, this difference was statistically insignificant.

It must be pointed out that in text books up until today the administration of conventional neuroleptica (in particular, haloperidol) is considered the method

of choice in the controlling of fearful or psychotiform LSD reactions (the so-called bad-trips or horror-trips) and thus comprehensive clinical experience is available. At the same time, however, it has to be noted that the administration of a strong working benzodiazepine always ought to be given first, because of the lower risk of side effects.

Benzodiazepines

Tests on animals Cook and Weidley (1957) carried out a series of tests to study the interaction between LSD and meprobamate in conditioned reflexes in rats. A dose of 500 mg benzodiazepine p.o. caused a non-specific blockade of all reflexes. LSD was an antagonist to this non-specific blockade at a dosage of 0.1 mg/kg s.c. By contrast, with administration of 0.5 mg/kg LSD, the effect was no longer observed. Meprobamate shows no interaction with LSD in cats (Elder et al., 1957). Later, Elder was also unable to find any effective interaction between meprobamate and LSD. A dosage of 50 mg/kg meprobamate following administration of LSD (no information about LSD dose and application method), influenced neither the LSD-induced rage reaction in cats, nor hyperthermia in rabbits.

Barnett (1971) reported experiences with LSD intoxication in Sydney, where diazepam (5–20 mg, p.o.) was the only medication used to relieve the LSD-induced symptoms. Levy (1971) also considers diazepam an efficient drug for the treatment of 'bad trips' induced by LSD.

Antidepressants

Tests on animals Appel and Freedman (1964) treated rats with 1.5 mg/kg tranylcypromine and 6 h later with LSD (crossover, $n = 4$, 130 μg/kg, i.v.). Compared with control experiments, the MAO inhibitor significantly prolonged the responses of the animals to learned behaviour (pressing on a bar for a reward of food).

Dixon (1968) treated rats with demethylimipramine (7.5–30 mg/kg, s.c.) 20 h between two LSD administrations (double blind, controlled, $n = 12$, 3 mg/kg, s.c.). A marked potentiation of LSD-induced behaviour change was observed.

Davis *et al.* (1977) carried out studies with a combination of antidepressants and LSD in rats. The authors gave chloroimipramine and desipramine (1, 2, 4, or 5 mg/kg), or imipramine and chlordesipramine (5 mg/kg), with LSD (30 μg/kg). All substances were given p.o. In addition, rats were injected i.p. with chlorimipramine and desipramine, followed by a further injection of 30 μg/kg [^{3}H]-LSD; then the level of both antidepressants in the brain was determined. At 5 mg/kg, all four antidepressants blocked the excitatory effect of LSD based on the acoustic startle response, which registers this parameter as a measure of

the sensory information flow and its rise or fall. In the dosage range of 1–5 mg/kg, chlorimipramine and desipramine were equally strong inhibitors of LSD, although they raised the level of LSD in the brain. Without additional LSD treatment, desipramine, imipramine, and chlordesipramine augmented the amplitude of the startle response; only chlorimipramine showed no such effect. The ability of chlorimipramine and desipramine to block the effects of LSD with respect to the studied index supports the hypothesis that the inhibition of raphe nuclei activity caused by both substances takes precedence over the property of LSD to increase the startle response directly by inhibition of raphe nuclei activity and to reduce the 5-HT availability. However, this does not explain the fact that the other tricyclic antidepressants also block this effect.

Fiorella *et al.* (1996) investigated the interaction between fluoxetin enantiomers and LSD (0.1 mg/kg, i.p.) in rats. The animals were trained using LSD as a discriminating stimulus (i.e. they could differentiate between LSD and saline). The dose–response relationship for LSD alone and in combination with (+)– or (–)–fluoxetin (2.5 mg/kg) was determined. In both cases, the dose–response relationship with varying dosages of LSD was shifted to the left, that is, the LSD effects were augmented. However, statistically significant changes were only found for the tests with the (+) enantiomer. These results are in contradiction to findings on the interaction of LSD and SSRIs in humans.

Winter *et al.* (1999) carried out investigations on substance discrimination with SSRIs and LSD in rats. Animals that were pretreated with LSD exhibited increased LSD-typical reactions following administration of all antidepressants (e.g. fluoxetin, fluvoxamine, and venlafaxine). The results led the authors to conclude that this was an addition of effects, rather than an actual potentiation. Eichenberger and Friolet (1957) injected iproniazid (100 mg/kg) into rabbits to test the interactions with LSD (open, controlled, $n = 12$, 10 μg/kg, i.v.) with regard to body temperature. The animals received iproniazid and, 30 min later, LSD, by which the rectal temperature was not affected.

Tests on humans The interactions between LSD and antidepressants are also of interest in relation to the mechanism of action of hallucinogens. After the previous decades had seen more precise characterization of the individual subtypes of the 5-HT receptors, selective studies, including ones with antidepressants, were undertaken. The concept of LSD–serotonin antagonism was pursued by numerous researchers (cf. Aghajanian, 1994).

Resnick *et al.* (1964) treated test subjects for a period of weeks with an MAO inhibitor (in animal studies, this results in an elevation of the serotonin concentration in the brainstem). Four men were exposed to six experimental situations in which they received LSD (open, randomized, crossover, $n = 4$,

40 or 75 μg, p.o.), either with or without pretreatment (2- or 5-week intake of 30 mg/d isocarboxazid). All the subjects reported LSD activity that was reduced or eliminated following the treatment with the MAO inhibitor. The parameters were interviews, behavioural observations, psychological tests, and physiological studies. A 3-day pretreatment with tranylcypromine (70 mg/d, p.o.) led to a pronounced reduction of typical LSD symptoms (open, cross-over, $n = 8$, 100 μg, p.o.) without influencing mydriasis (Marecek *et al.*, 1968). A single application of isocarboxazid, by contrast, had no influence on LSD effects in humans (DeMaar *et al.*, 1960).

If isocarboxazid is assumed to principally raise the level of indolamines in the brainstem, one might conclude that an excess of serotonin in the brainstem would prevent LSD effects from developing. In the framework of clinical studies on 11 (neurotic) patients, Grof and Dytrych (1965) investigated the interaction between antidepressants and LSD. The authors first treated the patients with 250–500 mg/d Niamid® i.v. (nialamide) and then 150–300 mg/d p.o. over a longer period of time (not specified). One day after discontinuing the antidepressant, various doses of LSD (open, controlled, $n = 11$, 150–500 μg, p.o.) were given. Doses of up to 400 μg LSD caused only minimal or no effects. In later tests, the interval between the last dose of nialamide and LSD was lengthened. The finding was that up to 14 days after discontinuing the antidepressant a strong resistance to LSD remained. In less well objectivized studies by Grof and Dytrych (1965), a weakening of the LSD effect was observed for a medium dose (not specified) of isocarboxazid or Nardil® (phenelzine). In an experiment with three neurotic patients, nialamide was given daily for 3 weeks up to an absolute dose of 3,500 mg. In this case, renewed administration of LSD resulted in no clinical symptoms. Strassman (1992) reports on a 38-year-old man with a medical history of intense hallucinogen consumption who received 20 mg/d fluoxetin for dysthymia and obsessions. The patient said he experienced a noticeable reduction in the potency of the LSD. The author posits a down-regulation of the serotonin receptors as the cause of the reduction in the activity.

As part of a retrospective study on the interaction between serotonergic antidepressants and LSD, Bonson *et al.* (1996) searched for test subjects on the Internet. Summarizing, the authors report on 33 people (8 women, 25 men) aged 15–37, who were all treated for at least 3 weeks with an antipressant before they consumed LSD. The effects were compared with previous experiences with LSD or with reports from people who had taken the same amount. Twenty-eight people out of this group received an SSRI. Of the 17 people who were given fluoxetin, a significant reduction in the effect was described in 88% of the cases. This reduction did not appear to depend on the dose of the SSRI. Sertraline (100–200 mg/d) was taken by nine subjects. With the exception of

one person, all of them noticed a significant reduction of the LSD action. Another person had knowingly not taken sertraline 36 h before taking the LSD; a noticeable reduction in the effect was still found. One month after discontinuation of fluoxetin, one person reported LSD effects at the familiar level.

The reduction in hallucinogenic and other LSD effects could be due to an adaptation of the serotonergic system, including changes to 5-HT_{1A} and 5-HT_{2A}/5-HT_{2C} receptors and the extracellular serotonin concentration, as well as the catecholamine system.

In further studies, Bonson and Murphy (1996) carried out interviews with 10 people who had previously had experience with LSD before again consuming LSD while taking a tricyclic antidepressant (TCA), an MAO inhibitor, or lithium. The five people who took a TCA all reported a potentiation of the LSD effects, saying the effects started sooner and physical and mental effects were intensified. The hallucinatory effects were described as more intense and multifaceted. Three subjects were treated with lithium alone or in combination with imipramine. They reported enhancement of all effects of the LSD. The combination of lithium and LSD appears to carry a particularly high risk potential. A temporary comatose state (leading to restitutio ad integrum) after the combined intake was reported (Middendorf, 2001). By contrast, the two people treated with MAO inhibitors showed almost no typical LSD effects after taking LSD.

Substances affecting the autonomic nervous system

Nearly all hallucinogens known today activate the sympathetic nervous system. Whether their effects are primarily caused by increasing the activity of a centrally generated sympathicotonia, or possibly also through effects on the autonomic nervous system, could initially not be determined unambiguously. What tends to contradict such a hypothesis is that similar autonomic effects can be achieved with various drugs without, however, causing mental alterations.

Reserpine

Reserpine belongs to the group of Rauwolfia alkaloids. It inhibits the sympathetic nervous system and is used as a sympatholytic and antipsychotic drug. Prolonged intake can deplete central stores of norepinephrine, dopamine, and serotonin and cause inhibition of their re-uptake.

Application of reserpine during LSD tests has shown that a dampening effect on sympathetic functions is not sufficient in animals and humans to antagonize the LSD actions. Although different test series used different testing methods and dosage schemes, there is general agreement that both substances exert inhibitory effects on each other (Purpura, 1956; Isbell & Logan, 1957; Elder & Dille, 1962). However, this is contradicted by neurophysiological studies

regarding the question of a noticeable interaction (Flugel & Bente, 1956; Takagi *et al*., 1958; Yui & Takeo, 1958; Elder & Dille, 1962).

Tests on animals Reserpine (5 mg/kg, s.c.) was given to mice 20 h before LSD (2 mg/kg, s.c.). This pretreatment led to a massive increase in excitatory LSD effects (Taeschler & Cerletti, 1957). Cook and Weidley (1957) studied the interaction between LSD and reserpine in rats. Reserpine (50 mg/kg, p.o.) causes a specific inhibition of conditioned reflexes. This effect is significantly antagonized by 0.1 mg/kg LSD and increases with increasing dosage (up to 0.5 mg/kg LSD). The action of LSD (2–65 μg/kg, i.v.) on the primary auditory response in rats was also antagonized by earlier application of reserpine (1.5 mg/kg, i.v.) in studies by Purpura (1956).

Appel and Freedman (1964) trained rats to press a lever to obtain food. This ability was strongly restricted by giving a high dose of LSD (crossover, 130 μg/kg, i.v.). By contrast, 40 μg/kg LSD i.v. had no influence on the learned reflex. A 5-day pretreatment with a total of 1.4 mg/kg reserpine heightened the LSD effects and the previously ineffective dose of 40 μg/kg LSD significantly affected the behaviour of the animals.

Dixon (1968) treated rats with reserpine (1.5–6.0 mg/kg, s.c.) 20 h before LSD application (double blind, controlled, $n = 12$, 3–5 mg/kg, s.c.). He was able to observe a marked potentiation of LSD-induced behaviour changes. The experimental animals exhibited higher aggression potential, with significantly reduced locomotor activity. Sugrue (1969) treated rats with i.p. doses of 5 mg/kg reserpine. The behavioural changes caused by administration of 2 mg/kg LSD were not influenced by this pretreatment, although the duration of the LSD effects was shortened significantly.

In tests of the effect of LSD on the body temperature of pigeons, Hoffman (1958) investigated the effect of LSD (open, crossover, 100 μg/kg, s.c.) in combination with reserpine. At dosages of 250 μg/kg, reserpine inhibited LSD-induced hypothermia.

Konzett (1956) gave reserpine (0.5 mg/kg, s.c.) to rabbits in order to test its influence on the blood sugar rise induced by LSD (0.15 mg/kg, s.c.). According to his results, reserpine lowered blood sugar levels in some animals, while it increased hyperglycaemia in others. Using different combinations of time intervals, Gogerty *et al*. (1957) studied the interaction between LSD and reserpine in LSD-induced hyperthermia in rabbits. Doses of 50 μg/kg LSD i.v. 2 h after 1 mg/kg reserpine i.v. caused a potentiation of the pyrogenic effects of LSD. When LSD was administered 6 hours after reserpine, the pyrogenic effect was undiminished. At an interval of 10 h between injections, the pyrogenic effect was reduced by 40–60%. In a follow-up experiment with cats,

the animals were given reserpine (0.5 mg/kg, i.v.) once a day for 7 days, with an additional i.v. injection of 400 μg/kg LSD on the seventh day. Compared with the cats that had not been pretreated with reserpine, these cats exhibited markedly more aggressive behaviour, followed by a catatonic-like state lasting around 48 h.

Eichenberger and Friolet (1957) injected rabbits with reserpine (0.1 and 1.0 mg/kg, i.v.) to study the interaction with LSD (open, controlled, $n = 12$, 10 μg/kg, i.v.) in affecting body temperature. Reserpine caused a powerful fall in body temperature. The rabbits' rectal temperature was raised by LSD 30 min after the reserpine-induced hypothermia. Depending on the time intervals between the applications, either reduction or increase of the fever effect was seen. Elder and Schellenberger (1962) studied the action of reserpine (2 mg/kg, i.v.) on LSD-induced hyperthermia in rabbits. Reserpine administration directly before the LSD application (open, controlled, 50 μg/kg, i.v.) potentiated the LSD effect, while a 1-day-long pretreatment with reserpine led to a significant diminution. Elder and Dille (1962) gave cats 0.5 mg/kg i.m. reserpine over a period of 6 days. This caused an inhibition of physical activity and appetite along with ataxia and miosis. After additive application of LSD (400 μg/kg i.v.) visual stimuli were no longer perceived, while tactile stimuli provoked a stronger reaction. After 30–60 min all the cats went into a catatonic-like state lasting for 24 h.

Tests on humans Isbell and Logan (1957) studied five groups with 12 subjects each (double blind, randomized, crossover, $n = 60$, 60 μg or 0.5 μg/kg, p.o.). The first four groups received 60 μg LSD 2 h after administration of reserpine (2.0, 5.0, or 7.5 mg p.o., or 6.0 mg i.m.). In none of the test series was reserpine seen to influence the LSD effects. In the fourth group, in 7 to 12 of the subjects gross tremor occurred, which had never been reported after application of LSD alone. In a further experiment, the subjects received 6.0 mg chlorpromazine i.m. and 2 h later 0.5 μg/kg LSD p.o. With this dosage scheme, a slight lessening of the clinical effects was observed.

Resnick *et al.* (1965) carried out studies on healthy men, but could not confirm the observations reported by Isbell and Logan (1957). First they tested the effect of LSD alone (open, crossover, $n = 3$, 75 μg, p.o.) on two different days. Then the subjects received a dose of LSD after a 2-week long pretreatment with 0.5 mg reserpine per day. For all the indices studied, a significant increase in the LSD effects was seen (as was in the study of Freedman *et al.*, 1964a). In addition to autonomic changes, some psychopathological and neuropsychological parameters were determined (including the apparent eye-level test and the Stroop colour-word test).

Phenoxybenzamine and other α-receptor blockers

Phenoxybenzamine is an alpha blocker and is used as a medication in neurogenic bladder disorders. In a certain dosage range, phenoxybenzamine induces a peripheral adrenergic blockade; central nervous effects are disputed.

Tests on animals Dixon (1968) demonstrated the influence of various α- and β-blockers on LSD-induced behaviour changes in rats. Following LSD administration (double blind, controlled, $n = 12$ per substance, 3–5 mg/kg, s.c.) the animals were given s.c. doses of 7.5–30 mg/kg phenoxybenzamine, dibenamine, propranolol, or pronethalol. A dose-dependent inhibition of the typical behaviour after LSD application was seen for all substances with the exception of dibenamine. This substance produced an inhibitory effect on the LSD-induced behaviour only at the highest dosage. Phenoxybenzamine showed a partial inhibitory effect on the studied indices at all doses. The two β-blockers propranolol and pronethalol, by contrast, only influenced the specific LSD-induced behaviour in the animals, but not the motor excitation.

In tests on rabbits, Elder and Schellenberger (1962) showed the inhibitory effect of phenoxybenzamine (10 mg/kg, i.v.) on LSD-induced hyperthermia (open, controlled, 50 µg/kg, i.v.). Hyperthermia was significantly inhibited at this dosage. The authors conjectured that phenoxybenzamine did not inhibit the effects of LSD on body temperature via a peripheral sympathetic blockade, as hexamethonium also exerted no influence, but that a central serotonin antagonism was more likely to be responsible.

Elder (1962, 1964) was also able to show a marked interaction between LSD and phenoxybenzamine in cats. Following i.v. administration of 15 mg/kg phenoxybenzamine, the test animals became relaxed and quiet. After 60 min LSD (300 µg/kg) was administered and the blood sugar level was measured (as the active parameter for both substances). A 50% reduction in the usual LSD-induced blood sugar rise was observed after 5–15 min. After 30 min the two curves crossed and after 1 h the combination of both substances generated a significantly stronger blood sugar increase than LSD alone. All other LSD effects were weaker or eliminated. The authors posited a depression of central sympathetic control areas as a possible mechanism of action of phenoxybenzamine on the effects of LSD.

Tests on humans The mental effects of LSD in healthy people were not influenced, according to Bertino et al. (1959b). The authors gave 0.25 mg/kg phenoxybenzamine as a 1-h infusion followed by LSD (double blind, cross-over, $n = 14$, 50 µg, p.o.). Even administration of phenoxybenzamine alone produced mild mental effects (e.g. lack of concentration, thought disorders,

as an adjuvant to LSD in psychotherapy. O'Reilly and Reich (1962) and Ruiz-Ogara *et al*. (1956), for instance, ended every LSD psychotherapy session with the administration of nicotinic acid. Whitaker (1964) routinely gave each patient nicotinic acid along with LSD during a therapy session.

Hoffer (1959) treated several subjects on a number of days with ascorbic acid (4 g p.o.) before administering LSD (there is no declaration of the design of the study, dose, or method of application). Another group received ascorbic acid when the LSD effects had reached a maximum. The author described that not the intensity, but the quality of the symptoms appeared to be changed. There was no reduction in the degree of changes in perception, but the subjects were able to concentrate better and apparently developed fewer paranoid thoughts. Twenty-four hours after the combined administration of LSD and ascorbic acid the subjects exhibited less fatigue and tension.

Steroids

Steroids are a large group of hormones that act by binding to DNA and affecting RNA transcription. They have a wide and varied range of application in medicine.

Tests on animals

Bergen *et al*. (1960) and Bergen and Pincus (1960) published studies on rats using various steroids. They administered 1 mg steroid i.p. over 4 days. On the fourth day, they gave an additional dose of 40 µg LSD. The controls received a placebo instead of the steroid. In addition to deoxycorticosterone (DOC), dehydrocorticosterone, corticosterone, 11-deoxycortisol, cortisone, and cortisol, they tested the animals with testosterone, Δ^4-androstenedione, androsterone, dehydroisoandrosterone, and aetiocholanolone, as well as the oestrogen estradiol and the C_{21} components pregnenolone, progesterone, and pregnanediol. The index was the climbing time up a vertical rope ending at a food source. LSD alone led to a significant rise in the climbing time just minutes after i.p. injection. The steroids alone had no influence on the climbing time. All the steroids (with the exception of oestradiol) generated a suppression of the LSD effect. The authors write that this suppression does not correlate with the hormonal action or potency of the steroids. Bergen *et al*. (1962) developed an *in vitro* experiment to address this issue. A method for the biotransformation of LSD using a homogenate of rat livers is described; to this, the author added the steroids in 1×10^{-7} molar concentration. Even such small amounts inhibited the metabolism of LSD, with cortisone being the strongest and dehydroepiandrosterone the weakest inhibitor. The authors proposed a hypothesis involving competitive action by LSD and steroids at identical cellular structures to explain the observations.

Selye (1971) gave rats 10 mg of a steroid p.o. twice a day. Later he tested the effectiveness of this pretreatment with 1 mg/kg LSD based on the parameter of LSD-induced dyskinesia. Pregnenolone-16α-carbonitrile, CS-1 (9-α-fluoro-11-β,17-dihydroxy-3-oxo-4-androstene-17-α-propionic acid potassium salt), ethylestrenol, norbolethone, prednisolone, triamcinolone, and oestradiol caused a slight reduction of the LSD-induced dyskinesia, while progesterone caused a significant reduction. Spironolactone, deoxycorticosterone acetate, oxandrolone, and hydroxydione did not influence the LSD effects (using the same dosage scheme).

In experiments with rabbits, Pierre and Cahn (1957) observed an effective inhibition or reduction of the EEG changes following acute or chronic LSD intake (50 μg/kg, i.v.) by administration of hydroxydione and methylandrostanolone. Cahn and Herold (1959) showed in rabbits that LSD (no exact dosages, etc., given) caused a loss of potassium and a retention of calcium in the brain, along with lowered glucose consumption, lowered phosphate uptake, increased lactate consumption, and reduced carbon dioxide production. Following application of hydroxydione, the potassium and phosphate values returned to the normal range. When the authors used methylandrostanolone, the substance principally antagonized the metabolic effects of LSD, but did not affect the lowering of the potassium levels in the brain.

Tests on humans Steroids, especially cortisone, are known to induce psychotic states in certain people. That spurred an interest by some researchers in a possible interaction between LSD and these hormones.

Clark and Clark (1956) carried out experiments on five schizophrenic patients. At first they tried, using intermittent administration on every third to fourth day, to find the individual threshold dose of LSD (60–130 μg), which led to the appearance of visual effects. This was followed by a 6-day phase of daily administration of 50 mg of cortisone. A renewed administration of the individual threshold dose of LSD produced the same effects as without steroid application. There is a discrepancy between these results and those of other authors, which might be explained by the often-described 'resistance' of schizophrenics to LSD effects (cf. Condrau, 1949). In addition, the problem of objectifying the subjective LSD effects must be considered.

In an experimental set-up by Abramson (1960), five healthy subjects in 49 tests were given various doses of prednisone (45–165 mg, p.o.). After 3–7 days, 15–50 μg LSD p.o. was given. Using questionnaires, the researchers found that during the administration of LSD alone, anxiety was the dominant feeling in the subjects. In 75% of the cases in which prednisone was given before LSD, anxiety was reduced markedly, without any influence on other typical LSD symptoms.

In a randomized study, 12 healthy subjects were treated with 600 mg progesterone or placebo, and 75 μg LSD or placebo (double blind, crossover, p.o.). Based on 11 tests of sensorimotor, perceptual, and conceptual behaviour, it could be shown that LSD effects were reduced by the oral administration of progesterone (Krus *et al.*, 1961). Some years later, Krus *et al.* (1967) used the same experimental design to do further tests with LSD and steroids. In addition to 75 μg LSD, the 12 healthy subjects received either 60 mg SC 10592 (3,17-β-diacetoxy-17 α-prop-1-ynyl-estra-3,5-diene) or 60 mg SC 7294 (3-β-propionoxy-17-β-hydroxy-17-α-ethylestr-4-ene) p.o. The results showed changes in sensorimotor, perceptual, and conceptual behaviour when LSD was given in combination with one of the two steroids. SC 7294 reduced typical LSD symptoms in four of the seven parameters; the other steroid only reduced symptoms in two of the parameters. The tests subjects themselves were not aware of changes.

Barbiturates

Barbiturates once found wide use as sedatives or hypnotics, but are mainly used today as anticonvulsants. They bind to the $GABA_A$ receptor complex, lengthening the open-time of the chloride ion channel. However, barbiturates also reduce the average inward sodium ion current.

Barbiturates were used successfully by many researchers to interrupt LSD reactions, but the mechanism of this interaction remained unknown. A possible explanation is that barbiturates depress the central nervous system.

Tests on animals In an experiment by Burton *et al.* (1957) mice were injected i.p. with LSD and pentobarbital (or hexobarbital). When the LSD was given an hour before the pentobarbital (60 mg/kg) or hexobarbital (100 mg/kg) anaesthesia, the effect of the barbiturate was prolonged by more than 30%. When 90 mg/kg pentobarbital i.p. was given simultaneously with various doses of LSD (0.7–9.0 mg/kg, i.p.), the duration of the narcosis increased with rising LSD dose; however, doses higher than 9.0 mg/kg caused no further lengthening. *In vitro* experiments, in which the oxidation of LSD was carried out in the presence and absence of various amounts of pentobarbital, showed that pentobarbital is an effective competitive inhibitor of LSD metabolism in the microsomal enzyme system.

In mice, a wide range of LSD doses (controlled, 2.5–80 mg/kg, i.p.) had no influence on the duration of hexobarbital narcosis (100 mg/kg, i.p.); only at 80 mg/kg was a slight lengthening observed (Brown, 1957). Salmoiraghi and Page (1957) showed that LSD (0.5–2 μg/kg, i.p.) lengthened by one-third of a hexobarbital narcosis. The prolongation of this narcosis by reserpine is blocked by LSD.

Eichenberger and Friolet (1957) injected rabbits with Numal® (aprobarbital 1.0 and 10 mg/kg) in order to test the interaction with LSD (open, controlled, $n = 12$, 10 µg/kg, i.v.). The animals received aprobarbital, followed 30 min later by LSD. The rectal temperature of the rabbits was not significantly affected.

Pretreatment of rats with 10 mg phenobarbital p.o. twice daily followed by 1000 µg/kg LSD led to a significant reduction of LSD-induced dyskinesia. A twice-daily dose of 6 mg phenobarbital over a period of weeks had no influence on the parameters investigated after LSD administration (Selye, 1971).

Tests on humans According to the results of experiments by Hoch (1955, 1956b) in humans, sodium amytal (200–500 mg, i.v.) partially inhibited the effects of LSD when it was given after the LSD began to act. It shortened the duration of action of LSD to 2–3 h. It particularly diminished the LSD-induced stress reaction, tension, and anxiety, as well as autonomic physical symptoms. However, the paper has no exact details on the subjects or the design of the experiment.

Clark and Bliss (1957) studied the effect of amobarbital on the mental effects of LSD. The authors gave six young men a dose of 0.3 g amobarbital 1.5 h before LSD administration (0.5–1.0 µg/kg, p.o.). This had no influence on the effects of the LSD.

Opiates

Tests on animals Cook and Weidley (1957) investigated the interaction between LSD and morphine in rats. The index used was the 'conditioned avoidance escape response' (CR). The authors were unable to show any antagonistic effect by 100–500 µg/kg LSD in the blockade of the CR through the influence of morphine (4–12 mg/kg). For high morphine doses, LSD had a slightly heightening effect on the CR. Dhawan and Gupta (1959) carried out tests on 150 rats to study the action of morphine in combination with LSD (50–500 µg/kg) on the response time following pain stimulus. The substances were applied s.c. and simultaneously. Using controls, it was shown that LSD has no actual analgesic power. The analgesic effect of a single dose of morphine alone was partially antagonized by LSD for more than 200 min (depending on the dose). The dose–response curve suggests a non-competitive antagonism. Tests related to the starting time and duration of analgesia showed no changes when additional LSD was given. The Straub tail reaction produced only by morphine and not by LSD could be curtailed by giving 50–500 µg/kg LSD s.c. after morphine administration (50 µg/kg). The authors conjectured a connection with serotonin levels in the brain, arguing that since morphine raises serotonin levels and the analgesic effects of morphine can be potentiated by serotonin, the antagonistic effect on morphine analgesia might be related to the anti-serotinergic properties of LSD.

Dhawan and Gupta (1961) carried out experiments on the interactions between apomorphine (a morphine derivative which has no opioid effects, being a dopamine agonist) and LSD in dogs. The animals were injected with 50 μg/kg LSD i.v. followed by the same amount of apomorphine. Vomiting caused by this substance could be inhibited by LSD. The combination of LSD and apomorphine led in some animals to transitory cataleptic states for 3–5 min. The LSD proved less effective as an antagonist to i.m. doses of morphine (1 mg/kg). In the above-named doses, LSD was ineffective towards ouabain (strophanthin), protoveratine (an alkaloid of white hellebore), and emetine (an alkaloid of ipecacuhana); all three substances caused vomiting in the animals. These results show that LSD can only act as an antagonist to substances whose emetic activity is controlled by the chemoreceptor trigger zone of the *Area postrema*. This led the authors to speculate about a direct interaction of LSD with morphine receptors.

Eichenberger and Friolet (1957) injected rabbits with morphine (1.0 and 10 mg/kg, i.v.) in order to test the interactions with LSD (open, controlled, $n = 12$, 10 μg/kg, i.v.) with regard to body temperature. The animals received morphine 30 min before LSD administration. While their rectal temperature was lowered with the low dose of morphine, 10 mg/kg morphine caused a potentiated effect. Dhawan (1960) studied further effects of morphine and its derivatives on LSD-induced hyperthermia in rabbits. Low doses of morphine (15 mg/kg, i.m.) were able to significantly lower the raised body temperature when they were given 2 h after LSD (crossover, $n = 40$, 50 μg/kg, i.m.). The same effects were obtained after administration of dihydromorphine (1 mg/kg, i.m.) and dihydrohydroxycodeine (5 mg/kg, i.m.), while nalorphine (5 mg/kg, i.m.) and apomorphine (250 μg/kg, i.m.) were not active against the LSD-induced hyperthermia. The two synthetic morphine derivatives, amidone (2.5 mg/kg, i.m.) and levorphan (1 mg/kg, i.m.), also proved to be ineffective with regard to the LSD antagonism.

Ethyl alcohol

Maracek and Bakalar (1967) studied the effects of ethanol (1 g/kg) in combination with LSD (open, crossover, $n = 7$, 100 μg, p.o.). Clinical observations could find no change in the LSD effects, but in a questionnaire patterned after Ditman *et al.* (1962) the perceptual changes were reduced. Pulse frequency was increased after combined administration, while pupil dilation and blood pressure were unchanged compared to intake of LSD alone. The authors concluded that ethyl alcohol is not an antagonist of LSD effects.

Azacyclonol (Frenquel)

Meratran (α-(4-piperidyl)-benzhydrol hydrochloride) is a central nervous system stimulant. It differs strongly from stimulants like amphetamine, in that

it has few cardiovascular and appetite-suppressing effects. It was used in trials for psychiatric disorders (e.g. depression, narcolepsy, dissociative disorders, and schizophrenia). The γ-isomer, azacyclonol (Frenquel), was known to be effective against delusions and hallucinations and so it was tested by Fabing (1955b) in connection with LSD effects. First, he gave two healthy patients 5–10 mg azacyclonol p.o. twice daily for a week. On the ninth day, the substance was administered simultaneously with 100 μg LSD p.o. The effects were compared with a control test with LSD alone. The combination of substances showed the same physiological effects as LSD (e.g. nausea, dry mucous membranes, perspiration, and abnormal vital functions). All these effects could have arisen from the corresponding mental reactions. However, the mental LSD effects were blocked. In a second experiment, six subjects were treated with azacyclonol (10–30 mg/d) before they were given LSD (double blind, controlled, $n = 6$, 100 μg, p.o.). With the exception of one person, no mental changes were described in the subjects.

According to several cases, azacyclonol (2 × 20 mg, i.v.) proved to be a reliable antagonist—even during maximum LSD effects (open, crossover, $n = 1$, 100 μg, p.o.) (Brown *et al*., 1955; Fabing, 1955a; Braun *et al*., 1956). Clark (1956) reported that the effects of LSD (single blind, crossover, $n = 5$, 100 μg, p.o.) remained unaffected by this substance in doses of 10–100 μg i.v. in schizophrenic patients.

By contrast, Isbell (1956) was unable to find any influence by azacyclonol on LSD activity (no details on experiment design and dosage). A year later, Isbell and Logan (1957) carried out tests with azacyclonol, along with chlorpromazine and reserpine in former morphine addicts. A dose of 20 mg azacyclonol p.o. was administered every 8 h for 7 days before LSD (double blind, randomized, crossover, $n = 12$, 60 μg, p.o.) was given. No influence of the pretreatment on the intensity of the LSD reaction was seen. Nor did i.v. administration of 40 or 60 mg azacyclonol 3 or 2 h, respectively, after various doses of LSD (2–3 μg/kg) have any measurable effects. Elder *et al*. (1957) were able to confirm this finding in another study (no details on experimental set-up and dosage).

Hydralazine and pentolinium

Hydralazine, like dihydralazine, belongs to the direct vasodilators. It causes smooth muscle relaxation (especially in the arterioles), lowering the peripheral resistance. Its ability to dampen central sympathicotonia is relatively weak. Pentolinium belongs to the family of ganglionic blocking agents. It works by binding to the acetylcholine receptor of adrenergic nerves and thereby inhibiting the release of noradrenaline and adrenaline. Blocking this receptor leads to smooth muscle relaxation and vasodilatation.

In tests on rabbits, Elder and Schellenberger (1962) studied the effect of pentolinium (5 mg/kg, i.v.) on the fever-producing action of LSD (controlled, 50 μg/kg, i.v.). At this dosage, pentolinium had no effect on the parameter when it was given 30 min before LSD.

Elder (1964) treated cats with 300 mg/kg LSD (i.v.) after they had received either pentolinium (5 mg/kg, i.v.) or hydralazine (2 mg/kg, i.v.). The index was blood sugar. While hydralazine alone only had a slightly elevating effect on blood sugar, it potentiated the LSD-induced rise. Pentolinium, by contrast, had no effect on this parameter on its own, but in combination with LSD, it reduced the LSD-induced blood sugar increase by around 50%.

Amphetamine derivatives

Amphetamine (α-methylphenethylamine) belongs to the group of synthetic substances based on phenylethylamine. The amphetamines appear to potentiate the effects of LSD, both increasing their intensity and prolonging their duration.

Tests on animals Foote *et al.* (1969) studied the influence of i.v. administered LSD (10 μg/kg) and amphetamine (1 mg/kg) on the activity of several brain areas in rats. In the studied raphe nuclei, 14 units responded to amphetamine with a rise in their spontaneous firing rate. LSD acted as an antagonist towards this effect. The cells could only be aroused again by amphetamine after the LSD effect had subsided. The remaining nuclei could be inhibited by LSD, but were generally insensitive to amphetamine.

Eichenberger and Friolet (1957) injected rabbits with amphetamine (0.2 and 1.0 mg/kg) to test its interaction with LSD (open, controlled, $n = 12$, 10 μg/kg, i.v.) with regard to body temperature. The animals were given amphetamine followed by LSD 30 min later. Their rectal temperature rose with amphetamine, and a dose-dependent enhancement of the LSD-induced body temperature rise was observed.

Tests on humans Methamphetamine (20–40 mg, i.v.) partially inhibited the effects of LSD when it was given after the start of LSD action. It also shortened the duration of action of LSD to 2–3 h, and modified the LSD-induced perceptual changes and disturbances in spatial–temporal orientation. The subjects became more open to the researchers and their actions were more related to reality than on LSD alone. However, Hoch (1955, 1956b) gave no exact details about the subjects and the experimental design.

Balestrieri (1957) gave amphetamine (20–30 mg, i.v.) to subjects at the height of LSD activity (open, $n = 8$, 200 μg, p.o.). The effects of both substances were intensified, but not qualitatively modified, according to his observations.

Ritalin is a sympathomimetic drug related to the amphetamines. It was used from 1954 to support psychotherapeutic treatment with LSD (Sandison & Whitelaw, 1957; Ling & Buckman, 1963). Today it is widely used to treat attention-deficiency hyperactivity disorder (ADHD).

In combination with LSD, ritalin caused, 15 min after i.m. injection, perceptual changes with withdrawal tendencies, distortion of the surroundings, and augmented mental activity. Changes in body image and proprioception were noted, as were changes of mood and affect. Ritalin modified the LSD effects and allowed the application of lowered doses of LSD in therapy (Ling & Buckman, 1963).

In the course of 370 LSD sessions, Kristensen (1962) additionally gave 23 seriously neurotic patients methylphenidate (Ritalin©, 30–50 mg, i.v.) during 220 sessions. Methylphenidate was administered additively at the height of the LSD effect (150 μg, p.o.). The two substances supported each other in their effects. The author developed the hypothesis that LSD caused a process of successively augmented tension, which was discharged by methylphenidate administration. Ling and Buckman (1963) gave methylphenidate 30 min after LSD and observed a reduction of LSD-induced anxiety. Leuner (1981) described the same effects as those described by Ling and Buckman (1963) and Kristensen (1962), based on many years of clinical experience with combination treatment using LSD and methylphenidate. Methylphenidate was administered when the LSD effect began to wane (see Figure 3.1).

α-Methylparatyrosine, tyrosine, and thyroxine

Tests on animals No interaction between α-methylparatyrosine and LSD was found in studies on mice (Menon *et al.*, 1977). Dixon (1968) treated rats with a single i.p. injection of 120 mg/kg α-methylparatyrosine 20 h before LSD administration (double-blind, controlled, $n = 12$, 3–5 mg/kg, s.c.). This substance is a potent inhibitor of catecholamine synthesis in the brain. It inhibited LSD-induced behaviour changes like wheezing, compulsive gnawing, and hypersalivating. It also inhibited locomotor activity. Sugrue (1969) treated rats with i.p. doses of 50 mg/kg α-methylparatyrosine. In contrast to Dixon's results, the behaviour changes induced by 2 mg/kg LSD were not influenced by the pretreatment. However, the onset of LSD effects was delayed and their duration shortened.

Davis *et al.* (1977) studied interactions of α-methylparatyrosine and LSD, administering 100 mg/kg tyrosine and 30 μg/kg LSD p.o. to test animals. The acoustic startle response in rats was used as an index. The effects of the LSD were not influenced by the tyrosine dose used. Following treatment with α-methylparatyrosine, the excitatory effects of LSD in rabbits were reduced.

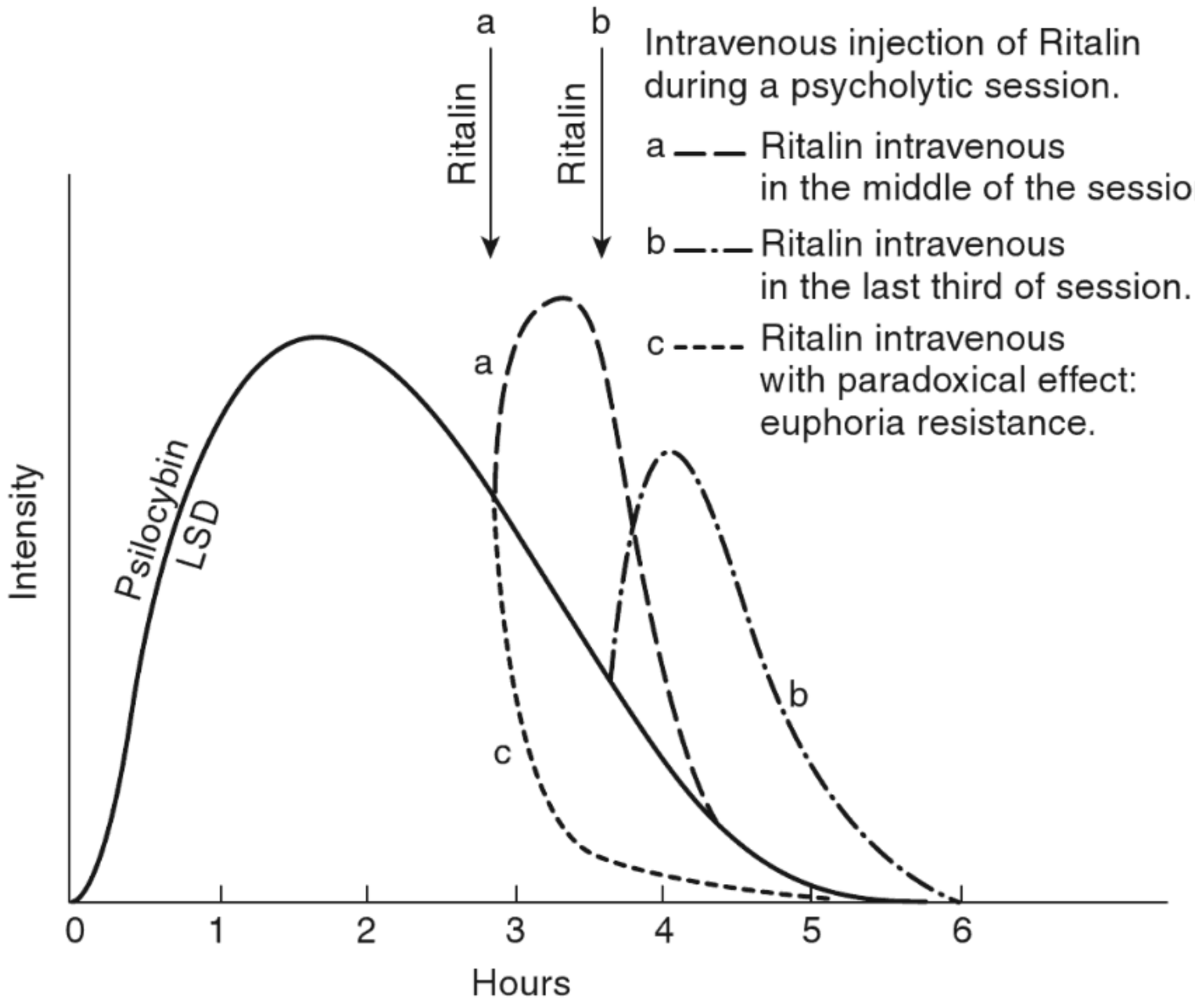

Fig. 3.1 Effects of an i.v. injection of methylphenidate (Ritalin©) during a psychotherapeutic session with LSD. Solid line shows the normal course of the LSD reaction. Lines a and b demonstrate the amplifying effects of methylphenidate. In some cases, decreases of the LSD reaction intensity were also found as shown by line c (from Leuner, 1981, p. 256).

Administration of L-DOPA with a peripheral decarboxylase inhibitor reinstated the effects. The LSD-induced hyperthermia was not affected (Horita & Hamilton, 1969, 1973).

Selye (1971) studied interactions of LSD and L-thyroxine. Rats were injected with the latter on a daily basis for several days at a dose of 200 μg s.c. The dyskinesia observed with LSD was unaffected by L-thyroxine.

Tests on humans Vojtechovsky *et al.* (1968) pretreated subjects with the two main precursors in catecholamine synthesis, L-tyrosine (5.0 g, p.o.) and L-DOPA (100 mg, p.o.), followed by LSD administration (open, crossover, $n = 6$, 518 or 683 μg, p.o.) and studied the interactions of the drugs. Combined administration of L-DOPA and LSD showed no differences in the psychopathological evaluation compared to placebo administration. Two hours after taking LSD, the subjects exhibited a rise in vegetative side effects such as mydriasis and pressor responses. By contrast, L-tyrosine was vegetatively inert after LSD administration. The mental effects of LSD were increased by 14% (augmented imaginative and memory activity, perceptual dysfunctions, and increased empathy).

Glutamate and succinate

Tests on animals Friedhoff and Abrams (1960) demonstrated antagonistic activity on the part of glutamine and glutamate, based on the pyrogenic effect of LSD in rabbits. Without LSD, these substances had no influence on the body temperature of the animals. However, the authors were able to show that glutamine and glutamate (25 mg/kg each, i.v.) significantly inhibited the fever-inducing effect of LSD (open, controlled, $n = 72$, 1 μg/kg, i.v.) when they were given first. The action of glutamine was faster, presumably, because glutamate did not pass the blood–brain barrier as easily, thus delaying its action.

Tests in humans Hoch (1965a) reported that the activity of neither glutamate nor succinate in humans could be antagonized by LSD. However, Hoff and Arnold (1954), Arnold and Hofmann (1955), and Arnold *et al.* (1957), using other administration techniques and dosages, observed a reduction of the extent of LSD-induced symptoms for both substances. They gave 20 g glutamate as an i.v. injection or 100 g p.o.; in another part of the experiment, 10 g succinate was given i.v. The theory of antagonism was based on the assumption of an interference by LSD with the functioning of the Krebs cycle and the repair of this malfunction due to the influence of glutamate or succinate.

Histamine and antihistamines

Yamada and Takumi (1956) studied the influence of histamine on various doses of LSD (open, crossover, 40–100 μg, p.o.) in nine psychiatric patients (no details of diagnoses given). Histamine (6 × 50 μg) was given at several different points in time after the beginning of LSD effects as i.v. infusions according to variable dosage schemes. In seven of nine cases, a marked normalization was seen in nearly all parameters influenced by LSD. The minimum dose sufficient to cause this effect was approximately 50 μg/10–15 min. The results of Bertino *et al.* (1959b) contradict those of Yamada and Takumi. Bertino *et al.* injected s.c. doses of histamine without finding any modification of the LSD symptoms (double blind, crossover, $n = 14$, 50 μg, p.o.).

Yamada *et al.* (1957) also showed the effects of an antihistamine on LSD activity. Ten series of experiments were carried out on seven healthy men who all received 25 μg LSD p.o. followed by 15–45 mg zinc oxide (Restamin©) i.v. In every case, the authors observed (despite the low LSD dose) an accentuation of the LSD symptoms compared with controls. In two subjects with 15 mg zinc oxide the effect proved to be mild and short, while in seven other cases [with] 30 mg a considerable enhancement lasting more than 80 min was seen. In addition, the authors claimed that zinc oxide had no influence on the total

duration of the LSD effect. As Yamada and Takumi (1956) had described a weakening of LSD effects by histamine, it appeared reasonable to suppose an enhancement of those effects by antihistamines.

Interaction with other substances (see Table 3.2)

Tests on animals Dixon (1968) treated rats 5 h before LSD administration (3–5 mg/kg, s.c.) with i.p. injections of 300 mg/kg disulphiram (tetraethylthiuram disulphide), which inhibits the conversion of dopamine to noradrenaline (and is used in the treatment of alcoholism). Here only a slight influence on LSD-specific behaviour changes was seen during the first 30 min after the onset of LSD action.

Dixon (1968) treated rats for 3 days before giving LSD (3–5 mg/kg, s.c.) with i.p. injections of 100 mg/kg d,l-parachlorophenylalanine. This is a potent inhibitor of serotonin synthesis in the brain (which does not influence the catecholamine concentration). The substance showed no influence on LSD-induced behaviour changes. By contrast, α-methylparatyrosine, an effective inhibitor of catecholamine synthesis in the brain (which, however, does not influence serotonin concentration) had a significant, inhibitory effect on the LSD effects.

Tests on humans In one test, Isbell *et al.* (1959c) carried out studies with the serotonin antagonist BAS (1-benzyl-2-methyl-5-methoxytryptamine) in non-psychotic addicted patients (double blind, crossover, $n = 15$, 0.5–1.5 μg/kg, p.o.). Taken on its own, 200 mg of this substance caused fatigue, confusion, and abdominal pains in all the subjects; vital functions were unimpaired. After these preliminary tests, 10 subjects received either 150 mg BAS or a placebo at various times before administration of LSD (0.5–1.5 μg/kg, p.o.) or placebo. The only observed effect was a reduction in the LSD-induced systolic blood pressure rise with BAS; all other typical LSD symptoms occurred with familiar intensity.

Effects of LSD in combination with the 5-hydroxytryptamine antagonists metergoline, pizotifen and cinanserin were studied in rats responding to a fixed-ratio 40 schedule of food presentation. All three antagonists attenuated the behavioral effects of LSD for both food presentations and pause intervals. The LSD response curve, that characterizes reinforcement, was shifted most by pizotifen (1.0 mg/kg), followed by cinanserin (20 mg/kg) and metergoline (1.0 mg/kg).

Hoffer and Callbeck (1960) gave a subject penicillamine (2 g, p.o.) in addition to LSD (100 μg, p.o.). According to the authors, this led to an attenuation of the affective component of the LSD action.

Table 3.2 Interactions of different substances on LSD effects

Substance	Species and conditions	Influence on LSD effects
Neuroleptics and tranquilizers		
Chlorpromazine	Humans and Animals	↓ Abramson, 1955; Schwarz *et al*., 1955; Eichenberger & Friolet, 1957; Isbell & Logan, 1957; Murphree, 1962
	Humans	↔ Clark & Bliss, 1957
	Conditioned behaviour in animals	↑ Halasz *et al*., 1969
Dimenhydrinate	Cats	↑ Elder *et al*., 1957
Promazine	Cats	↔ Elder *et al*., 1957
Tetrabenazine	Rats	↑ Appel & Freedman, 1964
Benzquinamide	Rats	↑ Appel & Freedman, 1964
Meprobamate	Cats	↔ Cook & Weidley, 1957; Elder *et al*., 1957; Elder, 1962
Diazepam	Humans	↓ Levy, 1970; Barnett, 1971
Antidepressants (ADs)		
Isocarboxazide	Humans	↓ Resnick *et al*., 1964; Grof & Dytrych 1965; Bonson & Murphy, 1996
Iproniazide	Rabbits	↔ Eichenberger & Friolet, 1957
Tranylcypromine	Humans	↓ Marecek *et al*., 1968
	Rats	↑ Appel & Freedman, 1964
Nialamide	Humans	↓ Grof & Dytrych 1965
Phenelzine	Humans	↓ Grof & Dytrych 1965
Fluoxetine	Humans	↓ Strassman, 1992; Bonson *et al*., 1996
	Rats	↑ Fiorella *et al*., 1996
Paroxetine	Humans	↓ Bonson *et al*., 1996
Sertraline	Humans	↓ Bonson *et al*., 1996
Tricyclic AD (Desipramin/ Imipramin)	Humans	↑ Bonson & Murphy, 1996
	Rats	↓ Davis *et al*., 1977; Dixon, 1968
Lithium	Humans	↑ Bonson & Murphy, 1996

Table 3.2 (continued) Interactions of different substances on LSD effects

Substance	Species and conditions	Influence on LSD effects
Substances affecting the autonomic nervous system		
Reserpine	Humans, one-dose	↔ Isbell & Logan, 1957
	Humans, pretreatment for two weeks	↑ Resnick *et al.*, 1965
	Body temperature in animals	↑ Gogerty *et al.*, 1957; Elder & Schellenberger, 1962 ↓ Hoffman, 1958; Elder & Schellenberger, 1962
	Behaviour in rats	↑ Appel & Freedman, 1964 u.a.; Dixon, 1968 ↓ Cook & Weidley, 1957; Purpura, 1956 u.a. ↔ Elder & Schellenberger, 1962
Phenoxybenzamine	Humans and animals (comparable conditions in all experiments)	↓ Elder, 1962, 1964; u.a.; Murphree, 1962 ↔ Bertino *et al.*, 1959b; Isbell *et al.*, 1959c
Dibenamine	Rats	↓ Dixon, 1968
Propranolol	Rats	↓ Dixon, 1968
Pronephtalol	Rats	↓ Dixon, 1968
Phentolamine	Rabbits	↔ Eichenberger & Friolet, 1957
Hexamethonium	Cats	↓ Elder *et al.*, 1957; Elder & Dille, 1962 u.a. ↔ Elder & Schellenberger, 1962
Atropine	Humans and animals (comparable conditions in all experiments)	↑ Forrer & Goldner, 1951 ↔ Miller *et al.*, 1957; Elder & Dille, 1962 u.a.
Scopolamine	Humans and animals	↔ Elder *et al.*, 1957; Isbell *et al.*, 1959c
Benactyzine	Rats	↓ Glow, 1959
Hydralazine	Cats	↑ Elder, 1964
Pentolinium	Animals	↓ Elder, 1964 ↔ Elder & Schellenberger, 1962
Nicotinic acid	Humans	↓* Agnew & Hoffer, 1955; Miller *et al.*, 1957 u.a.

(*cont'd*)

Table 3.2 (continued) Interactions of different substances on LSD effects

Substance	Species and conditions	Influence on LSD effects
Ascorbic acid	Cats	↓ Trulson *et al.*, 1985
	Humans	↓ Hoffer, 1959
Steroids		
Prednisone	Humans	↓ Abramson, 1960
SC 10592**, SC 7294**	Humans	↓ Krus *et al.*, 1967
Cortisone	Humans	↔ Clark & Clark, 1956
Desoxycorticosterone	Rats and *in vitro*	↓ *** ↔ Selye, 1971
Dehydrocorticosteron, Corticosterone, 11-Desoxycortisol, Cortisone und Cortisol	Rats and *in vitro*	↓ ***
Testosterone, Δ^4-Androstenedione, Androsterone, Dehydroisoandrosterone, Etiocholanolone	Rats and *in vitro*	↓ ***
Oestrogen	Rats and *in vitro*	↓ ***
Oestradiol	Rats and *in vitro*	↔ ***
Pregnenolone	Rats and *in vitro*	↓ ***, Selye, 1971
Progesterone	Humans, Rats, *in vitro*	↓ ***, Krus *et al.*, 1961; Selye, 1971
Pregnandiole	Rats and *in vitro*	↓ ***
CS-1**	Rats	↓ Selye, 1971
Oxandrolone	Rats	↔ Selye, 1971
Hydroxydione	Animals	↓ Pierre & Cahn, 1957; Cahn & Herold, 1959 ↔ Selye, 1971
Spironolactone	Rats	↔ Selye, 1971
Methylandrostanolone	Rabbits	↓ Pierre & Cahn, 1957; Cahn & Herold, 1959
Barbiturates		
Pentobarbital	Animals	↓ Burton *et al.*, 1957
Phenobarbital	Rats	↓ Selye, 1971
Amytal	Humans	↓ Hoch, 1955, 1956b
Aprobarbital	Rabbits	↔ Eichenberger & Friolet, 1957
Amobarbital	Humans	↓ Clark & Bliss, 1957

Table 3.2 (continued) Interactions of different substances on LSD effects

Substance	Species and conditions	Influence on LSD effects
Opiates		
Morphine	Animals, low dose of morphine	↔ Cook & Weidley, 1957; Eichenberger & Friolet, 1957, Dhawan & Gupta, 1961
	Hohe Dosis (ab 10 mg/kg), Tiere	↑ Cook & Weidley, 1957; Eichenberger & Friolet, 1957
	Animals, different doses of morphine	↓ Dhawan & Gupta, 1959; Dhawan, 1960
Dihydrohydoxycodeine, Dihydromorphine	Rabbits	↓ Dhawan, 1960
Nalorphine	Rabbits	↔ Dhawan, 1960
Amidone, Levorphan	Rabbits	↔ Dhawan, 1960
Apomorphine	Animals	↓ Dhawan & Gupta, 1961 ↔ Dhawan, 1960
Amphetamine(s)		
Amphetamine	Humans and animals	↑ Balestrieri, 1957; Eichenberger & Friolet, 1957 ↓ Foote *et al.*, 1969
Methamphetamine	Humans	↓ Hoch, 1955, 1956b
Methylphenidate	Humans	↑↓ Sandison & Whitelaw, 1957; Kristensen, 1962; Ling & Buckman, 1963 LSD-effects may be attenuated or amplified with identical conditions
Miscellaneous substances		
Thyroxine	Rats	↔ Selye, 1971
Tyrosine	Rats	↓ Dixon, 1968; Horita & Hamilton, 1969, 1973 ↔ Sugrue, 1969; Davis *et al.*, 1977; Menon *et al.*, 1977).
Para-chlorphenyl-alanine	Rats	↔ Dixon, 1968
Glutamate	Humans and animals	↓ Hoff & Arnold, 1954; Arnold & Hofmann, 1955; Arnold *et al.*, 1957; Friedhoff & Abrams, 1960 ↔ Hoch, 1956 a
Glutamin	Humans and animals	↓ Friedhoff & Abrams, 1960

(*cont'd*)

Table 3.2 (continued) Interactions of different substances on LSD effects

Substance	Species and conditions	Influence on LSD effects
Succinate	Humans	↓ Hoff & Arnold, 1954; Arnold & Hofmann, 1955; Arnold *et al.*, 1957 ↔ Hoch, 1956 a
Histamine	Humans	↓↑ Yamada & Takumi, 1956 ↔ Bertino *et al.*, 1959b
Anti-histaminics (Restamin**)	Humans	↑ Yamada *et al.*, 1957
Azacyclonol (Frenquel)	Humans (comparable conditions in all experiments)	↓ Fabing, 1955a,b; Brown *et al.*, 1955, Braun *et al.*, 1956 ↔ Clark, 1956; Isbell, 1956; Elder *et al.*, 1957; Isbell & Logan, 1957
BAS**	Humans	↔ Isbell *et al.*, 1959c
Penicillamin	Humans	↓ Hoffer & Callbeck, 1960
Disulphiram	Humans	↓ Dixon, 1968
5-HTP	Humans	↓ Pare & LaBrosse, 1963; ↑ Vojtechovsky *et al.*, 1967
Tryptophan	Humans	↑ Vojtechovsky *et al.*, 1967
Protease-Inhibitors Reverse-transcriptase-inhibitors	Humans	↑ Antoniou & Tseng, 2002

* nicht gesicherte Datenlage; fraglicher Befund,
** for chemical name cf. Text,
*** (Bergen *et al.*, 1960; Bergen & Pincus, 1960; Bergen *et al.*, 1962)

Antoniou and Tseng (2002) looked for interactions between antiretroviral drugs and LSD in humans. Protease inhibitors (PIs) and reverse transcriptase inhibitors (RTIs) influence the cytochrome P450 system by activating or inhibiting enzymes. Since the cytochrome P450 system may be involved in the metabolism of LSD in the liver (Inoure *et al.*, 1980; Cai & Henion, 1996), Antoniou and Tseng presume there is a rise in LSD concentration after the combined administration with PIs or RTIs.

Chapter 4

Psychological effects

Substances showing the kinds of effects discussed in the following sections have been most commonly described by terms such as 'hallucinogens', 'psycholytics', 'psychotomimetics', 'psychodysleptics', 'psychedelics', 'eidetica', or 'phantastica'. These terms refer to their specific psychosensoric effects in humans.

The mental effects of the 'classical' hallucinogens such as LSD, psilocybin, mescaline, and others are known to be highly complex. Because the psychological effects show high intra- and inter-individual variability and are influenced by a diversity of factors (see Figure 4.1), a number of models have been developed to conceptualize them.

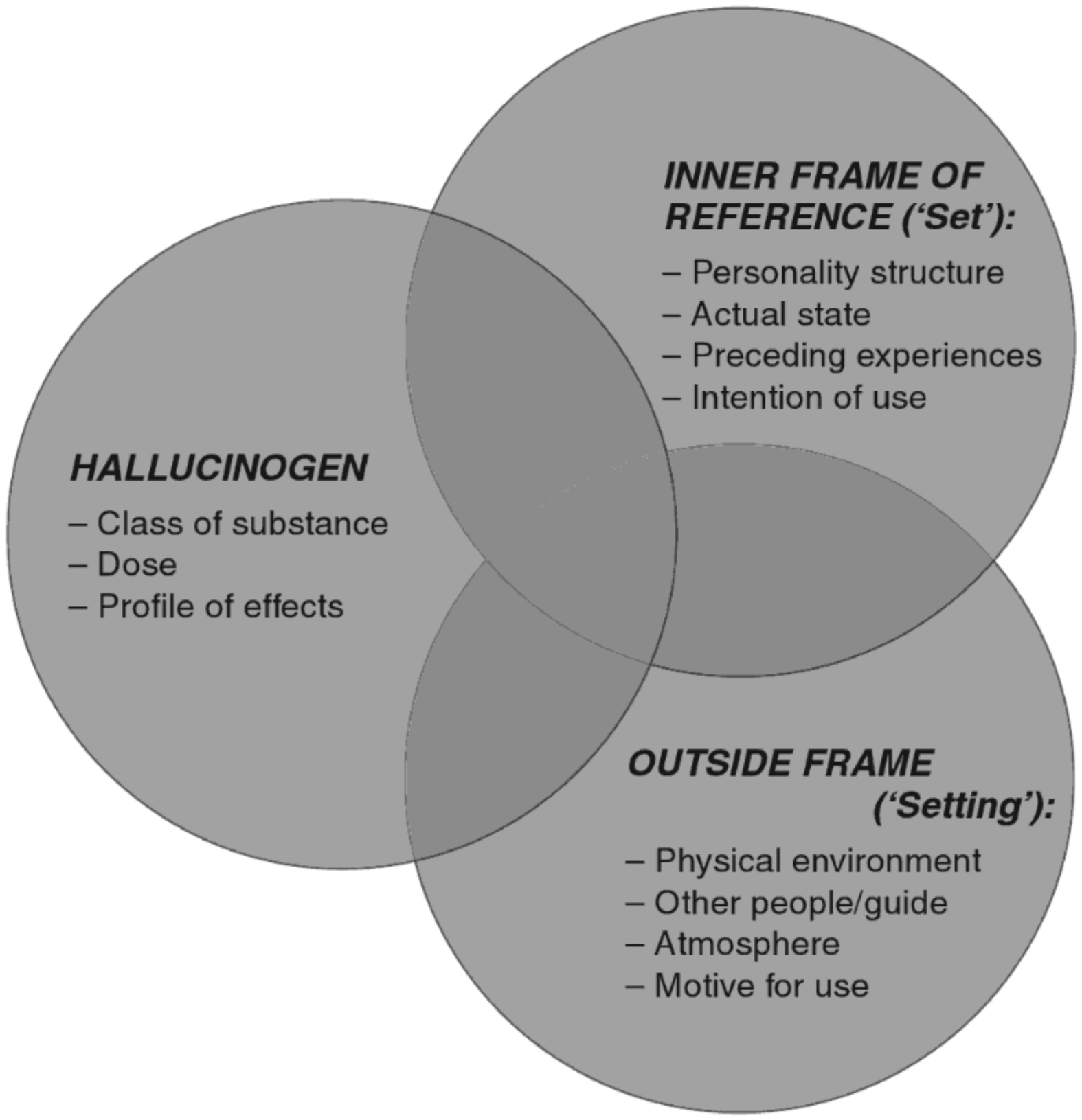

Fig. 4.1 Pharmacological and extrapharmacological factors influencing the reactions to hallucinogens (from Passie, 2005).

In the following account, the mental effects described from a psychopathological point of view, which in some respects may be not seem appropriate to describe the typical LSD experience.

An attempt has been made to group the symptoms in an order which—for those with no personal experience of hallucinogens—gives some indication of the increasing degree of difficulty involved in comprehending the psychoactive intoxication effects and the psychopathological collections of symptoms that arise.

Visual phenomena

In most descriptions and in most self-experimentation it is the optical phenomena which initially appear most impressive. However, there is no doubt that other components of the drug's activity intervene far more profoundly in the person's identity and experience of the world and that the visual effects are strongly influenced by them (e.g., emotionality). Thus it is possible—depending on the individual and the dosage—for the identification with the observed images to vary highly—on the one hand, a detached observation of an amusing or curious spectacle, or on the other, an enormously affective, overpowering experience of great verisimilitude which touches the personality, even with a fusion of the subject and the hallucinated object. This corresponds, in psychopathological terms, to the smooth transition from simple optical illusions and disorders of real perception to the so-called pseudo-hallucinations (i.e. without reality character and with a preserved reality assessment capability), all the way to true hallucinations (characterized by complete perception).

The contents of the optical phenomena are impressively—and often indescribably—rich; they range from simple elementary hallucinations (flickering, spraying, glittering, twirling, etc.) to multiple, multicoloured contours on real objects in the surroundings, to simple free-floating figures all the way to amazingly rich, filigree, and splendidly coloured ornamental or kaleidoscopic compositions. Particularly impressive is the continuous kinetic element, the flowing changes of the imagery in all three dimensions.

In addition to these more or less abstract–formal elements, entire progressions of figurative scenes may be experienced, with holistic, thematically linked images and concrete contents (e.g. objects, animals, people, mythical creatures, similar to the usual world of dreams) (cf. Fischer *et al.*, 1951b; Anderson & Rawnsley, 1954, and others).

Acoustic phenomena

These play only a marginal role and shall only be mentioned in passing here. 'Hearing voices' in the sense of schizophrenia is a considerably rarer effect.

and thread of the thoughts are lost or change frequently. In fact, at a low level of intoxication the train of thought is often accelerated, associatively relaxed to become a flight of ideas, or often erratic and incoherent. These changes are registered subjectively as effects of intoxication and often experienced as troublesome in the attempt to communicate the experience. At the peak of the individual intoxication phases, especially at higher doses, the centralization of the experience often leads, contrary to sluggishness or stagnation of the flow of thoughts, which remain or persevere around certain contents.

The content of thoughts is dependent on a variety of factors, such as the mood and affectivity, the optical imagery, the expectations and contact to the outside, as well as the personality itself. Interestingly, paranoid thoughts generally play only a subordinate role and are usually limited to fleeting paranoid responses. Systematic delusion is an absolute rarity (Stoll, 1947; Becker, 1949; Conndrau, 1949; DeShon *et al*., 1952).

Decoupling of perception and conceptual cognition

Conscious perception is limited to a tiny selection of the wealth of information about the surroundings received by our sensory organs. Some research suggests that the maximal information flow rate in conscious sensory perception is around 40 bits/s, many orders of magnitude below that taken in by the sensory receptors (Pöppel, 1989). The 18th century philosopher Leibniz had already realized that conscious perception from a limited selection of impressions stands before the background of a sea of non-conscious perceptions. A remarkable process of filtering and restriction takes place to limit the enormous potential amount of unconscious impressions to the culturally learned modes of experience.

Hallucinogenic drugs appear to interfere or counteract this reduction mechanism, enabling a more direct experience and perception beyond the limitations of learned cultural programmes (particularly the learned modes of space–time–verbalization identity). This may imply freedom from the confinements of learned, adaptive, survival-orientated perceptual mechanisms (which, however, usually remains available when the situation demands them). As the psychedelic artist Hoppy Hopkins says: 'You know what happens when you take acid; your conceptual framework gets sort of ripped apart for a few hours' (Roberts, 2008; p. 111). At the same time, it implies possible dangers due to unrealistic behaviour.

Changes of affectivity

Under the influence of LSD there is a dose-dependent, distinct activation of affectivity (Leuner,1962), which forms a basis for many of the modifications of

Chapter 5

Neuropsychological effects

Attention and concentration

Attention constitutes the perception's concentration on particular stimuli from our surroundings. It is a process of resource allocation of the limited processing capacity of the brain. Attention takes care of the perception of the environment, thoughts, and feelings, as well as personal behaviour and actions. Concentration means the willing focusing of the attention on a particular activity or a stimulus. Focusing means that attention is only paid to that being done or experienced at that moment, however, not to what has happened or is about to happen.

The measurement of attention and concentration can be carried out with different arithmetic tests or with the help of standardized tests (attention–pressure tests), which reflect the ability to carry out particular tasks over a certain length of time. The evaluation is made on the number of tasks completed and the number of mistakes that are made (see Table 5.1). A number of significant studies has to be mentioned here (cf. Table 5.1).

Anderson and Rawnsley (1954) described a reduction in the ability to concentrate in the majority of test subjects after LSD (open, $n = 23$, 10–600 μg, p.o.). Similar changes had already been found by Stoll (1947), Becker (1949), Condrau (1949), and DeShon *et al.* (1952). Systematic and standardized examinations were not undertaken at this early stage. Levine *et al.* (1955) tested their candidates using the Wechsler–Bellevue Test. It was possible to observe a clear impairment of attention and the ability to concentrate after the intake of LSD (open, crossover, $n = 21$, 50–200 μg, p.o.). Jarvik *et al.* (1955a) tested the influence on the concentration and attention of healthy candidates after LSD administration (open, crossover, $n = 12$, 50–100 μg, p.o.). Only two out of eight tests showed significant changes in the senses of a deterioration after 100 μg. Jarvik *et al.* (1955c) examined the effect of LSD (open, crossover, $n = 12$, 50–100 μg, p.o.) on Arithmetic Test Performance. The higher the dose, the lower the results. Primac *et al.* (1957) tested candidates with the Continuous Performance Test, before and after LSD administration (double blind, crossover, $n = 10$, 50–100 μg, p.o.). Coordination and attention were not restricted.

A dose of 1 μg/kg LSD (open, $n = 8$, p.o.) hindered candidates in repeating a row of numerals both forwards and in reverse order, which could speak

Table 5.1 Summary of LSD effects on attention and concentration measures

Dose	*n*	Test	Function	LSD effect	Reference
10–600 µg, p.o.	23	Bender Gestalt Test	Attention and concentration	↓	Anderson & Rawnsley (1954)
40 µg p.o.	11	Remembered numbers test (Wittenborn, 1943)	Attention and concentration	↓	Sloane & Doust (1954)
50–200 µg, p.o.	21	Wechsler Bellevue Scale	Attention and concentration	↓	Levine *et al.* (1955)
50–100 µg, p.o.	12	Whipple's Manual, Munsterburg Attention Test	Attention and concentration	↔ (↓)	Jarvik *et al.* (1955a)
75 µg p.o.	24	Stroop colour-word	Attention and concentration	↓	Wapner & Krus (1960)
75 µg p.o.	12	Stroop colour-word	Attention and concentration	↓	Krus *et al.* (1961)
50–100 µg, p.o.	12	Arithmetic Test Performance	Attention and concentration	↓	Jarvik *et al.* (1955c)
1 µg/kg, p.o.	8	Numeric series	Attention and concentration	↓	Orsini & Benda (1959)
2 µg/kg, p.o.	50	Easy mathematical additions and subtractions	Attention and concentration	↓	Weintraub *et al.* (1959)
1 µg/kg, p.o.	10	Reaction time apparatus	Attention and concentration	↔	Rosenbaum *et al.* (1959)
50–100 µg, p.o.	10	Continuous Performance Test	Attention and concentration	↔	Primac *et al.* (1957)
50 µg, p.o.	4	Porteus Maze Test	Attention and concentration	↓	Berlin *et al.* (1955)
75 µg, p.o.	20	Porteus Maze Test	Attention and concentration	↓	Krus & Wapner (1959)
75–100µg p.o.	34	Porteus Maze Test	Attention and concentration	↓	Aronson & Klee (1960)
72 µg, p.o.	20	Dual Pursuit Performance	Attention and concentration	↓	Silverstein & Klee (1960)

for the changing of the working memory's capacity to process (Orsini & Benda, 1959).

Similarly, the taking of LSD (open, controlled, $n = 50$, 2 μg/kg, p.o.) led to an accumulation of mistakes and slowed reactions in a word association test (see Table 5.2). Simple problem-solving is impaired, such as easy mathematical additions and subtractions, tests on spatial perception, awareness, and concentration and on the recognition of colours. Furthermore, it changed the ability to show differentiated reactions to emotional stimuli (Weintraub *et al.*, 1959).

According to Rosenbaum *et al.* (1959), LSD (open, crossover, $n = 10$, 1 μg/kg, p.o.) had no effect on the reaction time, which was measured by the reaction time apparatus (Rosenbaum *et al.*, 1957). According to the results from the Porteus Maze Test, which served to test the repression of impulsive behaviour to the benefit of critical planning, candidates lost the ability to carry out well thought through and adapted behaviour (Berlin *et al.*, 1955; Krus & Wapner, 1959; Aronson & Klee, 1960). Silverstein and Klee (1960b) tested subjects using the Dual Pursuit Performance Test (open, crossover, $n = 20$, 72 μg, p.o.). LSD significantly reduced the results of the tests during the early stages of the learning process, but less so in the later stages. The authors interpreted this to mean that it could be caused by a lack of ability to concentrate. But specific perceptual and coordination disturbances are also possible causes.

Abstract thinking

As in the case of psychotics, after the application of LSD and other hallucinogens one can find many forms of changes in ordered thinking and the contents of thought (Table 5.2). Anderson and Rawnsley (1954), for example, describe a disappearance of thoughts, a sudden break in a continuous line of thought under the influence of LSD (open, $n = 23$, 10–600 μg, p.o.). Afterwards it appeared to be no longer possible to retain more than one thought in the memory, the ability to concentrate changed, and the solving of simple mathematical problems seemed more difficult. Diverse test persons described confusing thought processes, speeded up trains of thought, or a loss of control over their thoughts. Similar changes in the train of thought after LSD intake were also reported by Stoll (1947), Becker (1949), Condrau (1949), and DeShon *et al.* (1952).

Fischer *et al.* (1951b) also found that a looser process of thinking occurred after LSD (open, $n = 32$, 60–130 μg, p.o.) was administered, and observed a slowing of the train of thought.

In addition to the previously mentioned tests, some other unconventional ones were carried out with informative results on the influence of the functions of thought by LSD.

Psycho- and visuo-motoric abilities

Psycho-motoric is defined as the interplay of psychic–mental–emotional experience and the experience of movement, that being the motoric (skills) of humans. Some significant studies regarding psycho-motoric and visuo-motoric abilities under the influence of LSD will be described here (Table 5.4). Abramson *et al.* (1955a) observed the effect of LSD (open, crossover, $n = 12$, 50 μg, p.o.) in two tests for hand–eye coordination and were unable to find any significant changes.

Abramson *et al.* (1955c) investigated the effects of LSD (open, crossover, $n = 12$, 50–100 μg, p.o.) on the manual and verbal reaction time to visual and acoustic stimulus (Pursuit Rotor Test, Dunlap Steadiness Test). The values of the verbal reactions time were significantly higher than under control conditions. Rosenbaum *et al.* (1959) were able to ascertain an improvement in the results in the Pursuit Rotor Test after LSD administration (open, cross-over, $n = 10$, 1 μg/kg, p.o.). Abramson *et al.* (1955d) gave human subjects tests which recorded manual reaction time ('simple reaction time to sound, simple

Table 5.4 Summary of LSD effects on psycho-motoric functions

Dose	*n*	Test	Function	LSD effect	Reference
50 μg	12	Hand–eye coordination	Psychomotor function	↔	Abramson *et al.* (1955a)
50–100 μg	12	Pursuit Rotor Test, Dunlap Steadiness Test	Manual + verbal reaction time to sound + light	↓	Abramson *et al.* (1955c)
1 μg/kg	10	Pursuit Rotor Test	Motoric functions	↑	Rosenbaum *et al.* (1959)
50–100 μg	12	Reaction time to sound + light, complex uncrossed + crossed reaction time	Manual + verbal reaction time to sound + light	↓	Abramson *et al.* (1955d)
50–100 μg	26	Bender Visual Motor Gestalt Test	Visual–motoric functions	↓	Abramson *et al.* (1955e)
50–100 μg	10	Digit Symbol Test, Tachistoscopic discrimination of circle size	Visual–motoric functions	↓	Kornetsky *et al.* (1957)

reaction time to light, complex uncrossed reaction time to light, complex crossed reaction time to light'), and verbal reaction time ('S had to read a series of 50 words naming common colours, and give the colours of a series of square coloured patches'), to visual and acoustical stimuli (open, crossover, $n = 12$, 50–100 μg, p.o.). The manual reaction time to acoustical stimuli was impaired the most. The verbal reaction time was also significantly extended with 50 μg LSD.

Abramson *et al.* (1955e) looked at the influence of LSD (open, crossover, $n = 26$, 50–100 μg, p.o.) on the results of the Bender Visual Motor Shape Tests for the evaluation of visuo-motoric functions as well as visual perception and memory. A significant worsening of the test results occurred after LSD administration.

Kornetsky *et al.* (1957) examined 10 test persons (double blind, crossover, $n = 10$, 50–100 μg, p.o.). The examiners found a dose-dependent impairment of performance in the Digit Symbol Test and in the Tachistoscopic Discrimination of Circle Size.

Judgement of time

Aronson *et al.* (1959) let the test subjects guess the time which had passed at a set moments after LSD administration (open, crossover, $n = 24$, 1–2 μg/kg, p.o.). On LSD the subjects overestimated the set time which had passed, that is, time seemed to go subjectively slower. Benda and Orsini (1959a) arrived at similar results (open, controlled, $n = 16$, 1 μg/kg, p.o.), just as did Boardman *et al.* (1957, double blind, crossover, $n = 4$, 0.75 μg/kg, i.v.). Fischer *et al.* (1951b) put these changes in the experiencing of time down to the larger data flow in the CNS under the effect of hallucinogens.

Estimation of weight, size, and spatial relations (see Table 5.5)

Rosenbaum *et al.* (1959) tested the change in the proprioception after LSD administration (open, crossover, $n = 10$, 1 μg/kg, p.o.) on healthy subjects. For this, the test subjects had to hold two standardized weights in their hands and judge which was the heaviest. No significant impairment of the judgement of weight could be found.

Weckowicz (1959) carried out a study on healthy test subjects to answer the question of the influence of LSD (double blind, crossover, $n = 18$, 35 μg, p.o.) on the perception of size. For this the subjects had to judge the size of an object. After LSD administration, no significant change was found. The only significant difference demonstrated was at the distance of 7.5 m between the

Table 5.5 Summary of LSD effects on proprioception, size constancy, and spatial relations

Dose	*n*	Test	Function	LSD effect	Reference
1 μg/kg	10	Weight Estimation	Proprioception	↔	Rosenbaum *et al.* (1959)
0.75 μg/kg	4	Size estimation	Size constancy	↓	Boardman *et al.* (1957)
35 μg	18	Size estimation	Size constancy	↓	Weckowicz (1957, 1959)
75 μg	24	Estimation of apparent horizon	Space localization	↓	Wapner & Krus (1959)
50–100 μg	12	Minnesota Paper Form Board Test, Thurstone Hand Test	Spatial relations	↓	Abramson *et al.* (1955b)

eye and object. Wapner and Krus (1959) also observed a trend towards misjudging the height with regard to the horizon, in test persons who received 75 μg of LSD (open, crossover, $n = 24$, p.o.).

Abramson *et al.* (1955b) tested die perception of spatial relations after LSD administration (open, crossover, $n = 12$, 50–100 μg), using the Thurstone Hand Test (THT) and the Minnesota Paper Form Board Test (MPFBT). A significant impairment was observed in spatial conception in the THT test after 100 μg LSD and in the MPFBT test even below 50 μg LSD.

Table 6.1 Reactions of relatives of schizophrenics to LSD (Anastasopoulos & Photiades, 1962)

	Normal reactions	Pathological reactions
Parents of schizophrenics (n = 20)	2	18
Siblings of schizophrenics (n = 44)	25	19
Healthy controls (n = 9)	9	0

reproduced and no changes were observed in the EEG during the period of LSD intoxication.

Five out of 8 subjects with psychomotoric epilepsy were treated with LSD (100–200 ug p.o.) and similar psychopathological phenomena which appeared during spontaneous seizures (visual hallucinations, sensation of 'blocking of thoughts', olfactory, taste and visceral sensations, preaccessual anxiety, and a peculiar head paresthesia), have been reproduced. The patients reported that they had the feeling that their usual ictal episode was repeated. There was no sign of epileptic activation registered in the EEG during the assays.

Chapter 7

Long-term and untoward effects of LSD use

Psychological long-term effects

From the beginning of the 1960s, criticism of LSD use increased—also in the framework of psychotherapeutic sittings or in experiments. The dangers of a retreat from social life or a drug-induced psychosis were considered great and the treatment of such cases difficult. LSD was made illegal, and pharmacological research, as well as its use in psychotherapy, strongly declined. Nevertheless, possible long-term effects always continued to be controversially discussed. Hollister (1967) put forward the proposal that LSD generally did not induce a permanent psychosis, but was preferentially taken by emotionally labile people and this personality structure was a disposition to the triggering of temporary psychotic conditions. Freedman (1968) criticized Hollister's position, in as much as to say that one ought not to make a connection between emotional disorder and drug taking, only because LSD leads to acute changes in mood and inner drive.

To plot the psychological long-term effect of LSD, McGlothlin *et al.* (1968) designed a long-term study on healthy subjects (double blind, controlled, $n = 70$, 200 μg, p.o.). Over the days following LSD application, the subjects were given a course of psychological tests. The application was repeated three times within a few weeks. After 6 months, the tests were carried out again and compared with the results from before the application of the substance. The tests used for evaluation were the Cattell's Severity of Judgement Test, the Marlowe–Crowne Social Desirability Scale and elements out of the California F Scale, the Rokeach´s Dogmatism Test, and the Levinson's Traditional Family Ideology Scale. In tests on personality, opinions, and values, the subjective evaluation of many test persons in the experimental group, that 'positive' changes had occurred, could only be partially confirmed.

The sensibility towards aesthetics was tested using three tests (Bulley Test, Graves Design Judgement Test, Barron–Welsh Scale). According to the results, 62% of the experimental group had more understanding for music and 42% for art. This was reflected in the frequent visiting of musical events and museum

visits, as well as the purchase of sound recordings, such as on records or tapes. According to their self-information, creativity increased in 24% of the test group.

In a further study by McGlothlin *et al.* (1970a), the experimental group received a middle-sized dose of LSD (double blind, controlled, $n = 70$, 200 μg, p.o.) three times; in a control group test subjects were given 20 mg of amphetamine and in a second control group subjects received a subliminal dose of 25 μg LSD. In the projective tests, the Holtzman Inkblot Test proved to have lightly raised values after 2 weeks and significantly heightened values after 6 months, from the test persons in the experimental group. The TAT showed relatively non-uniform changes and the Rosenzweig–Picture–Frustrationstest was slightly lowered half a year after three applications of 200 μg LSD. Otherwise, no significant changes occurred.

In a further study, the test subjects of the study mentioned above were evaluated by McGlothlin *et al.* (1970b), using the passivity scale of Morris' Ways-to-live Test. In the 200 μg–LSD group, significantly increased values were found after 2 weeks; however, none was found after 6 months. The Marlowe–Crowne Social Desirability Scale served as the measuring stick of self-perception and after 6 months showed clear losses in the test group.

In summary, it can be said that these studies prove that psychologically stable individuals under controlled test conditions show no unwanted long-term effects from taking LSD.

The low incidence of long-term effects through the experimental use of LSD is particularly impressive, if one takes Cohen's (1960) series of observations into account. He reported numerous studies, in which the following symptoms are attributed to the long-term effect of LSD: migraine attacks, influenza, paraplegia, suicide attempts, and rashes. All these reactions also occurred in people who were serving as control subjects, however, and unknown to them were receiving placebos.

Surveys on risks of experimental and psychotherapeutic use

In LSD psychotherapy, certain possibilities pertaining to complications have been investigated. For this, the complications that had occurred in 9,300 patients during the 1950s (USA; Cohen, 1960) and 1960s (England; Malleson, 1971) were retrospectively registered. These and the results of a more recent catamnestic test using psycholytic therapy (1988–1993) on 121 patients by Gasser (Switzerland; 1997) is described here (see Table 7.1).

Cohen (1960) sent questionnaires to 62 testers, who had used either LSD or mescaline in experimental examinations or in psychotherapy, and received

problems are the selectivity of the test subjects, the non-objective quantity of LSD ingestion, as well as the unrecorded ingestion of other drugs at the same time. Blacker *et al.* (1968) interpreted EEG abnormalities and McGlothlin *et al.* (1969) interpreted a little impairment in the ability of abstraction as a sign of minimal brain damage. The latter compared the results of neuropsychological tests in a group ($n = 14$) who had either taken LSD (150–20 μg) in a psychotherapeutic setting (150–20 μg), or in a non-medical framework at least 20 times, with another group ($n = 16$) of people, who had consumed no illegal substances (except for cannabis). Both groups had a quasi-identical WAIS intelligence quota (Halstead–Reitan Neuropsychological Test). In the Halstead category test (non-verbal measurement of memory, as well as the ability to recognize abstract principles), the number of mistakes was 57.3 (LSD consumers) compared with 39.6 (controls). The Shipley–Hartford Test (measurement of general intelligence) and the trail-making A-Test (psychomotoric coordination) showed up no differences between the groups. By contrast, one test group scored somewhat better results than the other in the Trail-making B Test (spatial orientation). Other tests on visual perception and spatial orientation (Porteus Maze, Minnesota Percepto-Diagnostic Test, Witkin´s Embedded Figures) showed no differences. It is to be noted critically that the results of such small groups cannot be taken as relevant for real substance-induced effects.

Wright and Hogan (1972) tested chronic LSD consumers using the Halstead–Reitan Neuropsychological Test. For this they compared 20 test subjects, who regularly took LSD (on average 30 times, with estimated doses of between 100 and 300 μg), with controls without substance misuse. In the WAIS Comprehension Test, the group of LSD takers performed significantly worse. On the other hand, they showed significantly better results than the control in the WAIS Information Test. The results from the Halstead Category Test and the Mean Impairment Index showed no significant differences.

With regard to scientific evidence, it can be concluded that research on the possible long-term effects of LSD has gained no consistent evidence for permanent morphological or physiological effects on the human organism. Studies suggesting otherwise were drawing conclusions from casuistics and studies that were inadequately controlled or much too small (Halpern & Pope, 1999).

Dependence

The definition according to ICD-10 of the evidence of a 'dependence syndrome' is implied by the following criteria:

> A strong desire (urge), to consume the substance; a loss of control of its ingestion

Physical withdrawal symptoms and the consequent renewed ingestion.

Tolerance development and dosage increase.

Usual social behaviour is not upheld.

Previous interests and other 'pleasures' are neglected.

Despite psychological impairment, organ damage, and social disadvantages, consumption continues.

Based on biological behavioural criteria, the substance, being a positive reinforcer, plays a decisive role in the development of dependence and addiction.

If a particular substance functions as a positive reinforcer, and physical symptoms appear when taking is stopped or reduced, one talks of physical dependence. Psychological dependence, on the other hand, manifests itself as 'not being able to stop' and as an unavoidable desire (craving).

In people and animals, LSD creates a stable tolerance after repeated ingestion (e.g Isbell *et al.*, 1955; Abramson *et al.*, 1956; Rothlin & Cerletti, 1956); however, it does not lead to a physical dependence (Jaffee, 1965; McIsaac *et al.*, 1970). It appears to be difficult to prove the dependency potential of LSD based on retrospective data. Above all, the problem are the reliability of the data from LSD consumers and the dose, or purity of illegal LSD. For these reasons, researchers have used animal models for the determination of the dependency potential of different substances (e.g. Schuster & Thompson, 1969). In these models, the psychological and physical components of dependence were evaluated. There were no indications in any of the tests that LSD created physical dependence (Thompson & Pickens, 1970; Poling & Appel, 1979). LSD was unable to be used as a positive reinforcer in animal studies; on the contrary, LSD even works as a negative reinforcer (Hoffmeister & Wuttke, 1973; Hoffmeister, 1975).

Even during the most popular period of LSD taking, with the exception of some described individuals (Blacker *et al.*, 1968), almost all LSD consumers followed a very sporadic usage of LSD. This indicates, besides biochemical and biobehavioural data, that the dependency potential of these substances ought to be low. Despite this, the ICD-10 and DSM IV lists a psychological dependence on hallucinogens such as LSD as an entity of disease.

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Author Index

Aase, J.M *et al.* 79
Abramson, H.A. *et al.* 32, 84, 89, 101, 114, 143–4, 145
Adey, W.R. *et al.* 82–3
Aghajanian, G.K. 43
Aghajanian, G.K. and Bing, O.H. 32
Aghajanian, G.K. *et al.* 33
Agnew, N. and Hoffer, A. 112
Alexander, G.J. *et al.* 78
Anastasopoulos, G. and Photiades, H. 149
Anden, N.E. *et al.* 33, 35
Anderson, E.W. and Rawnsley, K. 60, 67, 137, 139
Antoniou, T. and Tseng, A.L. 128
Appel, J.B. and Freedman, D.X. 87, 88, 89–90, 100, 103, 107
Arnold, O.H. *et al.* 22, 23, 64, 122
Arnold, O.H. and Hofmann, G. 122
Aronson, H. *et al.* 144
Arvanov, V.L. *et al.* 37
Auerbach, R. and Rugowski, J.A. 78
Axelrod, J. *et al.* 24, 25, *26*

Bachini, O. *et al.* 62
Bajgar, J. *et al.* 70
Balestrieri, A. 88, 90, 120, 148
Balestrieri, A. and Fontanari, D. 87, 89
Barac, G. 58
Barnett, B.E. 103
Belsanti, R. 56–7, 65
Benda, P. and Orsini, F. 144
Bender, L. 68–9
Bente, D. and Itil, T. 61
Berenstein, L. and Otero, T. 67
Bergen, J.R. *et al.* 113
Bergen, J.R. and Pincus, G.G. 113
Beringer, K. 4
Bertino, J.R. *et al.* 109, 112, 122
Bhattacharya, B. 54
Bick, Y.A.E. 77
Bignami, G. 82
Bircher, R.P. *et al.* 54
Blacker, K.H. *et al.* 156
Bleuler, Manfred 5
Bliss, E.L. *et al.* 81
Boardman, W.K. *et al.* 144
Bonson, K.R. *et al.* 105
Bonson, K.R. and Murphy, D.L. 106
Borsy, J. *et al.* 86
Boyd, E.S. *et al.* 28, 29, 31
Bradley, *et al.* 63
Brattemo, C.E. and Lassenius, B. 141
Brengelmann, J.C. *et al.* 95
Broer, H.H. *et al.* 98
Brown, B.B. 63
Buckholtz, N.S. *et al.* 84
Burton, R.M. *et al.* 115

Cahn, J. and Herold, M. 114
Callieri, B. and Mariani, E. 71
Canezin, J. *et al.* 30
Carlson, V.R. 63
Cates, N. *et al.* 98
Cerletti, A. 15
Cerletti, A. and Konzett, H. 19
Chessick, R.D. *et al.* 55
Cholden, L.S. *et al.* 84, 87, 89, 148
Christoph, G.R. *et al.* 44, 46
Clark, L.D. 118
Clark, L.D. and Bliss, E.L. 102, 111, 116
Clark, L.D. and Clark, L.S. 114
Cohen, M.M. *et al.* 73
Cohen, S. 9, 142, 152–3
Cohen, S. and Ditman, K.S. 153
Collu, R. *et al.* 57
Condrau, G. 147
Cook, L. and Weidley, E. 99, 103, 107, 116
Corey, M.J. *et al.* 76
Costa, E. and Zetler, G. 96, 97

DaPrada, M. *et al.* 44, 96
Davis, M. *et al.* 103, 120
DeGiacomo, U. 147
Delphaut, J. and Lanza, M. 54
DeMaar, E.W.J. *et al.* 32
DeShon, H.J. *et al.* 139
Dhawan, B.N. and Gupta, G.P. 116–17
Diab, I.M. *et al.* 24, 48
DiMascio, A. *et al.* 53, 54
DiPaolo, J.A. *et al.* 78
Dishotsky, N.I. *et al.* 73, 74
Dixon, A.K. 100, 103, 107, 120, 123
Djahanguiri, B. and Giuti, N. 100

Egozcue, J. and Irwin, S. 73, 76
Eichenberger, E. and Friolet, B. 100, 104, 108, 116, 117, 119
Elder, J.T. 67, 109, 119
Elder, J.T. and Dille, J.M. 108, 110
Elder, J.T. *et al.* 99, 103, 110, 118
Elder, J.T. and Schellenberger, M.K. 108, 109, 110, 119
Ellis, S. 67
Elmadijan, F. *et al.* 97
Evarts, E.V. 59

Bahan dengan hak cipta

Fabing, H.D. 118
Fang, C. *et al.* 26–7
Feld, M. *et al.* 66
Fiorella, D. *et al.* 104
Fischer, R. *et al.* 139, 144
Foote, W.E. *et al.* 119
Forrer, G. and Goldner, R. 53, 55, 59, 66, 110
Fox, C.L. *et al.* 72
Freedman, D.X. 93, 151
Freedman, D.X. and Aghajanian, 86
Freedman, D.X. *et al.* 82
Friedhoff, A.J. and Abrams, B. 122

Gaddum, J.H. 93, 94
Ganong, W.F. *et al.* 96
Garson, O.M. and Robson, M.K. 73
Gastaut, H. *et al.* 60
Geber, W.F. 78
Geiger, L.E. and Cervone, P. 59
Geiger, R.S. 65
Giberti, F. and Gregoretti, L. 101
Gillett, E. 82
Gillin, J.C. *et al.* 91, 92
Ginsberg, Allen 11
Ginzel, K.H. and Kottegoda, S.R. 97
Ginzel, K.H. and Mayer-Gross, W. 89
Glennon, R.A. *et al.* 35, 39
Glow, P.H. 111
Goetz, P. *et al.* 77
Gogerty, J. 107
Goldberger, M. 70
Goldstein, L. *et al.* 61
Gonzalez-Maeso, J. *et al.* 39, 50
Gouzoulis-Mayfrank, E. *et al.* 36
Graham, J.D.P. and Khalidi, A.I. 97
Green, W.J. 80
Greig, M.E. and Gibbons, A.J. 70
Grof, S. 9, 52, 55, 135
Grof, S. *et al.* 105
Grof, S. and Halifax, J., *The Human Encounter of Death* 71

Halasz, M.G. *et al.* 100–1
Haley, T.J. *et al.* 23
Halpern, J.H. and Pope, H.G. 155
Hamilton, C.L. 82
Hanaway, J.K. 78
Harkonen, P. and Konttinen, Y. 66
Hassler, O. 66
Heacock, R.A. and Mahon, M. 21
Healy, J.M. and Van Houten, P.L. 79
Hertle, F. *et al.* 53, 66
Hirschhorn, I.D. and Cohen, M.M. 74
Hoagland, H. 23
Hoagland, H. *et al.* 68, 96
Hobson, J.A. 80
Hoch, P.H. 116, 119, 122, 148
Hoch, P.H. *et al.* 101–2
Hoff, H. and Arnold, O.H. 25, 122
Hoffer, A. 28, 32, 84, 113
Hoffer, A. and Callbeck, M.J. 123
Hoffer, A. and Osmond, H. 96, 112
Hoffman, R.A. 100, 107
Hofmann, Albert 10, 12
  discovery of LSD 3–4
  studies on psychometric effectiveness 15, *16*
Holliday, A.R. *et al.* 63
Holliday, A.R. and Sigurdson, T. 56
Hollister, L.E. 58, 62, 97, 151
Hollister, L.E. and Hartman, A.M. 68
Hollister, L.E. and Moore, F.F. 97
Hollister, L.E. and Sjoberg, B.M. 66
Hollunger, G. and Persson, S.A. 45
Horita, A. and Dille, J.M. 55
House, R.V. *et al.* 72
Hoyer, D. *et al.* 39
Hulten, M. *et al.* 77
Huxley, A. 10

Idänpään-Heikkilä, J.E. and Schoolar, J.C. 77
Inoue, T. *et al.* 28
Irwin,S. and Egozcue, J. 73
Isbell, H. 118
Isbell, H. *et al.* 15, 83–4, 88, 89, 91, 110, 111, 123, 140
Isbell, H. and Jasinski, D.R. 91
Isbell, H. and Logan, C.R. 101, 102, 108, 118

Jarvik, M.E. and Chorover, S. 83
Jarvik, M.E. *et al.* 74, 101, 137
Jonas, S. and Downer, J.C. 83

Kast, E.C. and Collins, V.J. 71
Kato, T. and Jarvik, L.F. 78
Kehr, W. and Spekenbach, W. 45
Keller, H.H. *et al.* 96
Keup, W. 26
Kies, M.W. *et al.* 58
King, A.R. *et al.* 93
Klee, G.D. *et al.* 32, 95
Klette, K.L. *et al.* 30
Knoll, J. and Vizi, E.S. 90
Knoll, M. *et al.* 64
Koella, W.P. *et al.* 83
Konzett, H. 67, 100, 107, 110
Kornetsky, C. *et al.* 144
Krill, A.E. *et al.* 64
Kristensen, K. 120
Krus, D.M. *et al.* 115
Kurrasch-Orbaugh, D.M. *et al.* 41

Lanz, U. *et al.* 25–6
Leary, T. 10
Leuner, H. 6, 9
Levine, A. *et al.* 137, 140, 142
Levy, G. 103
Liddell, D.W. and Weil-Malherbe, H. 96, 97
Lienert, G.A. 142

Bahan dengan hak cipta

Lin, R.C. *et al.* 94
Ling, T. and Buckman, L. 120
McGlothlin, W.H. *et al.* 151–2, 154
Mahler, D.J. and Humoller, F.L. 82, 91
Malleson, N. 153, 154
Maracek, P. and Bakalar, E. 117
Marona-Lewicka, D. *et al.* 48, 51
Matussek, N. and Halbach, A. 90
Meltzer, H.Y. *et al.* 58
Menon, M.K. *et al.* 120
Messiha, F.S. *et al.* 97
Metzler, C.M. 24
Miller, A.I. *et al.* 111, 112
Miltrani, L. *et al.* 64
Miura, T. *et al.* 65
Monroe, R.R. *et al.* 61–2
Murphree, H. 101, 110
Muzio, J.N. *et al.* 80

Nandy, K. and Bourne, G.H. 70–1
Neuhold, K. *et al.* 55
Nichols, C.D. *et al.* 38, 39
Nielsen, E.B. 43
Nielsen, J. *et al.* 75
Niwaguchi, T. *et al.* 28, 30
Nosal, G. 78

O'Brien, C.P. *et al.* 72
O'Reilly, P.O. and Reich, G. 113
Ostfeld, A.M. 64

Pahnke, W.N. 135–6
Pallotta, A.J. and Ward, J.W. 72
Palmer, G.C. and Burks T.F. 96
Pare, C.M. and LaBrosse, E.H. 95
Payne, J.W. 55–6
Persson, S.A. 44, 45, 97–8
Persson, S.A. and Johansson, H. 45
Peters, D.A.V. and Tang, S. 84
Pfeiffer, C.C. *et al.* 61
Pierce, P.A. and Peroutka, S.J. 35
Pieri, M. *et al.* 96
Pierre, R. and Cahn, J. 114
Prieto, P.A. *et al.* 62
Primac, D.W. *et al.* 137, 140
Purpura, D.P. 107

Ray, O.S. and Marrazzi, A.S. 100
Resnick, O. *et al.* 104–5, 108
Rinkel, M. *et al.* 58, 60, 68, 97
Robinson, J.T. *et al.* 76
Rodin, E. and Luby, E. 63
Rosenbaum, G. *et al.* 139, 144
Rosenberg, D.E. *et al.* 91, 92
Rothlin, E. 54, 67
Ruiz-Ogara, C. *et al.* 113

Sackler, A.M. *et al.* 57, 65, 96
Sadzot, B. *et al.* 37
Safer, D.J. 81
Salmoiraghi, G.C. and Page, I.H. 115
Sanguineti, I. *et al.* 60
Savage, C. 147
Schwarz, B.E. *et al.* 101, 149–50
Selye, H. 114, 116, 121
Shagass, C. 63, 64
Shanthaveerappa, T.R. *et al.* 71
Shibusawa, K. *et al.* 72
Shirahashi, K. 61
Silva, M.T.A. *et al.* 89
Silverstein, A.B. and Klee, G.D. 139, 140–1
Simonovic, M. and Meltzer, H.Y. 91
Siva Sankar, D.V.S. *et al.* 58, 67–8, 95, 98
Slaytor, M. *et al.* 30
Sokoloff, L. *et al.* 60, 67
Solms, H. 17
Sparkes, R.S. *et al.* 75
Stace, W.T. 135
Stolk, J.M. *et al.* 44
Stoll, A. 3, 4
Stoll, A. *et al.* 82, 83
Strassman, R.J. 105, 153–5
Strassman, R.J. *et al.* 92
Sugrue, M.F. 107, 120

Taeschler, M. and Cerletti, A. 107
Tijo, J. *et al.* 76
Tilson, H.A. and Sparber, S.B. 86, 90
Torda, C. 81
Torre, M. and Vergani, E. 67, 68
Toyoda, J. 80
Trulson, M.E. *et al.* 83, 112
Turner, W.J. *et al.* 89
Twarog, B.M. and Page, I.H. 93

Vojtechovsky, M. *et al.* 95, 121
Vollenweider, F.X. *et al.* 36, 41, 46

Wagner, J.G. *et al.* 24–5
Wapner, S. and Krus, D.M. 145
Warkany, J. and Takacs, E. 78
Watts, V.J. *et al.* 46
Weckowicz, T.E. 144–5
Weltman, A.S. and Sackler, A.M. 57, 66
Whitaker, I.H. 113
Winter, J.C. 86
Winter, J.C. *et al* 104
Wolbach, A.B. *et al.* 87
Wooley, D.W. and Shaw, E.N. 65, 93
Wright, E.M. 24
Wright, M. and Hogan, T.P. 156

Yamada, T. *et al.* 122
Yamada, T. and Takumi, A. 122

Zsigmond, E.K. *et al.* 70

Bahan dengan hak cipta

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Subject Index

Please note: page numbers in *italics* refer to Figures and Tables.

absorption 21
abstract thinking, effect of LSD 139–41
accommodative convergence, effect of LSD 55–6
acetylcholinesterase activity 69–71
acetyl-lysergic acid diethylamide (ALD) 17
acidic phosphatase activity 71
acoustic effects 130–1
adenylate cyclase, effect of LSD 45
adrenal glands, effect of LSD 57, 65, 66, 96
adrenaline, interactions with LSD 96–7
adrenergic receptors 47
  LSD affinity *49*
adverse reactions 153–4
  risk factors for 154–5
Adverse Reaction to Psychedelic Drugs, R.J. Strassman 153–4
aesthetic sensibility, long-term effects of LSD 151–2
affect, effect of LSD 133–4
affective disorders, effect of LSD 148–9
ALD (acetyl-lysergic acid diethylamide) 17
alkaline phosphatase activity 71
allergic reactions, protective effect 71–2
α-methylparatyrosine, interaction with LSD 120, 123
α-receptor blockers, interaction with LSD 109–10
alpha rhythm changes 60, *62*
American psychology, paradigm shift 7
N-amide-substituted amide of lysergic acid 19
amidone, interaction with LSD 117, *127*
amobarbital, interaction with LSD 116, *126*
amphetamines
  cross-tolerance with LSD 85, *85*, 89–90
  EEG changes 61
  interaction with LSD 119–20, *127*
amytal, interaction with LSD 116, *126*
analgesic effects 71
anaphylaxis, protective effect 71–2
androstenedione, interaction with LSD *126*
ania3 expression 38
anticoagulants, interaction with LSD 66
antidepressants, interaction with LSD *124*
  tests on animals 103–4
  tests on humans 104–6
antidiuretic effect 58
antihistamines, interaction with LSD 123
anxiety, LSD-assisted psychotherapy 12
apomorphine, interaction with LSD 117, *127*
aprobarbital, interaction with LSD 116, *126*
arc expression 38
ascorbic acid, interaction with LSD 112, 113, *126*
ataxia 59
atropine, interaction with LSD 110–11, *125*
attention, effects of LSD 137–9
auditory evoked potentials (AEPs) 64
autism, effects of LSD ix, 148
autonomic effects
  in schizophrenics 148
  tolerance 82
autonomic nervous system activation 59
azacyclonol (Frenquel), interaction with LSD 117–18, *128*

bad trips 154
  treatment 99, 102–3
barbiturates, interaction with LSD 115–16, *126*
BAS (1-benzyl-2-methyl-5-methoxytryptamine), interaction with LSD 123, *128*
benactyzine, interaction with LSD 111–12, *125*
Bender Visual Motor Shape Test performance, effect of LSD *143*, 144
benzodiazepines, interaction with LSD 103, *124*
benzquinamide, interaction with LSD 102, *124*
β-blockers, interaction with LSD 109, *125*
beta rhythm changes *62*
biochemical effects
  on carbohydrate metabolism 67–8
  on cholinesterase activity 69–71
  on fatty acids 69
  on phosphate metabolism 68–9
biogenic amines, interaction with LSD 96–8
blind subjects, pseudohallucinations 64
blood–brain barrier 24–5, *26*
blood cells, effects of LSD 65–6
blood pressure, effect of LSD 53, 59, 97
body perception, effects of LSD 131–2
body temperature, effect of LSD 53, 54–5
body weight changes 57
BOL *see* 2-bromo-lysergic acid diethylamide (BOL)

مادة محمية بموجب حقوق النشر

brain
  animal studies, distribution of LSD 22, 23–4
  interaction of different regions 39–41, *42*
  see also deep brain structures; dopamine receptors; 5-HT receptors
brain cells, effects of LSD 65
2-bromo-lysergic acid diethylamide (BOL) 15, 88, 98
  comparison with LSD *18*
  cross-tolerance with LSD *85*, 88–9

carbohydrate metabolism, effects of LSD 67–8
carcinogenic potential 72–3
cardiovascular effects 52–4
catecholamines, interaction with LSD 96–8
cats
  distribution of LSD 24
  tolerance 82–3
C/EBP- β expression 39
cephalin–cholesterol flocculation test 57
cerebral blood flow, effect of LSD 60
c-fos expression 38
'chemical psychosis' 147
chemistry 14–15
chlordesipramine, interaction with LSD 103–4
chlorimipramine, interaction with LSD 103–4
chlorpromazine, interaction with LSD *124*
  animal studies 99–101
  human studies 101–2
  metabolism inhibition 31
cholinesterase activity, effect of LSD 69–71
chromosomal damage 73
  in germ cells 76–7
  and impure LSD 74–5
  in vitro studies 73–4
  in vivo studies 74
  mutagenic effects 77–9
  and pure LSD 75–6
CIA, funding of research 7
cinanserin, interaction with LSD 123
citalopram, interaction with LSD 44
compulsion disorders, effect of LSD 148–9
concentration 137
  effects of LSD 137–9
conditioned reflexes, effect of LSD 82
confiscation of LSD, 1960s 10
consciousness, alterations of 134
'consciousness-expansion' 10
Continuous Performance Test, effect of LSD 137, *138*
convulsive ergotism 3
Coramin® (nicotinic acid diethylamide) 3
cortico-striato-thalamo-cortical (CTSC) loops 40, *42*
cortisone, interaction with LSD 113, 114, *126*
creativity enhancement 10
  long-term effects 152
cross-tolerance 85
  with amphetamine 89–90
  with ergotamine 90
  with mescaline 86–7
  with psilocybin 87–8
  summary of studies *85*
  with tetrahydrocannabinol 91
  with tryptamine 91–2
CS-1, interaction with LSD 114, *126*

dark adaptation curves, effect of LSD 63
deep brain structures
  electrical activity studies 61
  nucleus accumbens 47, 48
  nucleus caudataus, LSD binding 48
  nucleus reticularis 36, 40–1
  see also raphe nuclei; thalamus
dehydroepiandrosterone, interaction with LSD 113
delayed reactions 153–4
delusions 133
Delysid® 4
demethylimipramine, interaction with LSD 103
deoxycorticosterone acetate, interaction with LSD 114, *126*
dependence x, 47, 156–7
depersonalizing effects 131
derivatives of LSD *16*
  structure–activity relationships 15–21
Deseril (1-methyl-lysergic acid butanolamide) 15, 17
  cross-tolerance with LSD *85*, 90
  distribution 23
desipramine, interaction with LSD 103–4
detection in body fluids 32–3
diazepam, interaction with LSD 103, *124*
dibenamine, interaction with LSD 109, *125*
Digit Symbol Test performance, effect of LSD *143*, 144
Dihydergot® 3
dihydro-(+)-LSD 19
dihydrohydroxycodeine, interaction with LSD 117, *127*
dihydromorphine, interaction with LSD 117, *127*
dihydroxy-LSD 30
3,4-dihydroxyphenylacetate (DOPAC), striatal concentrations 97–8
dimenhydrinate, interaction with LSD 102, *124*
N,*N*-dimethyltryptamine (DMT) 38
  cross-tolerance with LSD *85*, 91
discovery of LSD 3–4
distribution 13, 21–4
  blood–brain barrier 24–5
  protein binding 25–6
distribution volume 24

مادة محمية بموجب حقوق النشر

disulphiram, interaction with LSD 123, *128*
DMT *see* *N*,*N*-dimethyltryptamine
L-DOPA (L-3,4-dihydroxyphenylalanine)
  brain concentration, effect of LSD *45*
  interaction with LSD 121
dopamine, interaction with LSD 96, 97–8
dopamine receptors 44–7
  interaction with serotonin receptors 47–8
  LSD affinity *49*
  summary of actions of LSD 50
dosage 32
  lethal 51
  lower oral threshold 51
dream experience, effect of LSD 80
Dual Pursuit Performance test, effect of LSD *138*, 139
duration of effects 21
  see also long-term psychological effects

ego functions, alterations of 134
egr-1 expression 38–9
egr-2 (*krox-20*) expression 38–9
electrocardiography (ECG) studies 54
electroencephalography (EEG) studies 60–2
  during sleep 80
elimination 13
elimination half-life 32
embryotoxicity
  animal studies 77–8
  human casuistics 78–9
endocrine effects 57–8
eosinopenia 65, 66
epilepsy, effects of LSD 149–50
epinephrine *see* adrenaline
ergometrine 3
ergonovine 14
ergotamine 2–3
  cross-tolerance with LSD *85*, 90
ergotism 3
ethyl alcohol, interaction with LSD 117
ethylestrenol, interaction with LSD 114
etiolcholanolone, interaction with LSD *126*
euphoria, effect on catacholamine levels 98
evoked potentials, effect of LSD 62–4
excretion 31–2
'experimental psychosis' 147
eyes
  effects of LSD 55–6
  electrical stimulation 64

fatty acid mobilization 69
fear, effect on catecholamine levels 98
fertility 77
'fifth freedom' 11
flashbacks 155
flovoxamine, interaction with LSD 104
fluoxetine, interaction with LSD 44, 104, 105, *124*
focusing 137
follicle-stimulating hormone levels 58
Food and Drug Administration (FDA), drug confiscations 10
gangrenous ergotism 3
gastrointestinal effects 56–7
gene expression changes 38–9
germ cells, chromosomal damage 76–7
glucose metabolism, effects of LSD 67–8
glucuronic acid excretion 57
glutamate
  cortical levels 37, 40, 41, 50
  interaction with LSD 122, *127*
glutamine, interaction with LSD 122, *127*
goats, tolerance 83
growth hormone levels, effect of LSD 57–8
gustatory phenomena 131

half-life 13, 32
hallucinations 130
Hallucinogenic Persisting Perception Disorder (HPPD) 155
hallucinogenic substances, research approval process 11–12
halogenized LSD 19
haloperidol, inhibition of dopaminergic effects 44
Halstead category test, effect of LSD use 156
Halstead–Reitan Neuropsychological Test, effect of LSD use 156
hand–eye coordination, effect of LSD 143
'hearing voices' 130
heart rate, effect of LSD 53
hexamethonium, interaction with LSD 110, *125*
hexobarbital, interaction with LSD 115
hippocampus 41
'hippy' movement 11
histamine, interaction with LSD 98, 122–3, *128*
histidine, interaction with LSD 98
Hofmann, Albert 10, 12
  discovery of LSD 3–4
  studies on psychometric effectiveness 15, *16*
Holtzman Inkblot Test, effect of LSD 152
'holy fire' 3
5-HT (5-hydroxytryptamine; serotonin) 48–9
  in anaphylactic reactions 71–2
  interaction with LSD 93–*4*, 98
  relationship to dreaming 79–80
5-HT_{2A} agonists, study of hallucinogenic activity 50
5-HT receptors 44
  effects of LSD 33, *34*, 35
  5-HT_{1A} receptor *34*, 40, 41, 43
  5-HT_{1B} receptor 43
  5-HT_{1C} receptor *34*, 39, 44

مادة محمية بموجب حقوق النشر

5-HT receptors (*cont.*)
5-HT_{1D} receptor 43–4
5-HT_2-receptor family 35–9
interactions in different brain regions 39–41
5-HT_{2A} receptor *34*, 35–7, 40, 41, 43, 50
and cortical glutamate levels 37
down-regulation 38
and gene expression 38–9
and phosphatidyl inositol turnover 37
5-HT_{2C} receptor *34*, 39, 41
interaction with dopamine receptors 47–8
LSD affinity *49*
role in tolerance 84
subtypes *35*
summary of actions of LSD 48–51
Human Encounter of Death, The, S. Grof and J. Halifax 71
Hydergine® 3
hydralazine, interaction with LSD 118, 119, *125*
hydrated LSD combinations 19
hydroxydione, interaction with LSD 114, *126*
13/14-hydroxy-LSD *29*, 30
hydroxyskatol 21
5-hydroxytryptophan, interaction with LSD 94–5, *128*
hyperacusis 131
hyperamnesias 135
hyper-reflexia 59
hypersensitivity 59
hypersuggestibility 132
hypervigilance 134

identity disorders 131
Iκβ-α expression 38
ILAD-1 expression 39
illegal synthesis 11
imipramine, interaction with LSD 103–4
immediate adverse reactions 153, *154*
immune system, effect of LSD 72
impure LSD, chromosomal damage 74–5
indolamines, 5-HT_2 receptor affinities 50
indole metabolism, effect of LSD intake 32
indol nucleus, 4-substitution 20
inhibitory effect, serotonin 49–50
inhibitory GABA neurons, effect of 5-HT_{2A} receptor activation 40
intellectual functions, effect of LSD 141–2
Intelligenz-Struktur Test, effect of LSD *141*, 142
interactions *124–8*
with endogenous substances
biogenic amines 96–8
5-hydroxytryptophan 94–5
serotonin 93–4
with exogenous substances 98–9
α-methylparatyrosine 120, 123
α-receptor blockers 109–10
amphetamine derivatives 119–20
antidepressants 103–6
antihistamines 123
ascorbic acid 112, 113
atropine 110–11
azacyclonol (Frenquel) 117–18
barbiturates 115–16
BAS 123
benactyzine 111–12
benzodiazepines 103
benzquinamide 102
chlorpromazine 97–100
dimenhydrinate 102
disulphiram 123
L-DOPA 121
ethyl alcohol 117
glutamate 122
hexamethonium 110
histamine 122–3
hydralazine 118, 119
nicotinic acid 112–13
opiates 116–17
D,L-parachlorophenylalanine 123
penicillamine 123, *128*
pentolinium 118–19
protease inhibitors 128
reserpine 106–8
reverse transcriptase inhibitors *128*
scopolamine 111
steroids 113–15
succinate 122
tetrabenazine 102
L-thyroxine 121
L-tyrosine 119–20
intermittent reactions 154
intramuscular injection 21
intraocular pressure, effect of LSD 56
intraspinal injection 21
intrathecal injection 21
intravenous injection, pharmacokinetics 21
iodine-LSD 19
iproniazide, interaction with LSD 104, *124*
isocarboxazid, interaction with LSD 105, *124*
isolysergic acid 14

ketone body excretion 58
kidney
effects of LSD 58
LSD concentration, animal studies 22
Konzentrations-Leistungtest performance, effect of LSD 142
krox-20 (egr-2) expression 38

LA 111 (lysergic acid amide) 17
lacrimation, effect of LSD 56

Bahan dengan hak cipta

LAE 32 (lysergic acid monoethylamide) 17, *29*
  as a metabolite of LSD 30
laughter, uncontrollable 131
LD_{50} 51
LEO (lysergic acid ethyl-2-hydroxyethylamide) *29*, 30
lethal dose 50, 51
leucocyte count 65–6
levorphan, interaction with LSD 117
Liddell, D.W. and Weil-Malherbe, H. 96, 97
Lienert, G.A. 142
light-sensitivity 14
light stimulation, enhancement of LSD-induced effects 62–3
lithium, interaction with LSD 106, *124*
liver
  LSD concentration, animal studies 22
  metabolism of LSD 28
liver function 56–7
locus coeruleus 36, 48–9
long-term psychological effects 151–2
  dependence 156–7
  flashbacks 155
  permanent CNS changes 155–6
  after psychotherapeutic use 152–5
low voltage fast sleep (LVFS), effect of LSD 80
[^{3}H]-LSD 35
lumi-LSD 19
luteinizing hormone levels 58
lymphocyte count 65, 66
lysergic acid, chemical structure *20*
lysergic acid amide (LA 111) 17
lysergic acid ethyl-2-hydroxyethylamide (LEO) *29*, 30
d-lysergic acid L-propanolamide 3
lysergic acid monoethylamide (LAE 32) 17, *29*
  as a metabolite of LSD 30
lysergic acid morpholide (LSM) 17
lysergic acid pyrrolide 19

MDMA ('Ecstasy')
  combination with LSD 6
  psychotherapeutic use 12
mechanism of action 13
melting point 14
memory, hyperamnesias 135
meprobamate, administration with LSD 103, *124*
meratran 117–18
mescaline 20
  Aldous Huxley's use 10
  cross-tolerance with LSD 86–7
metabolic effects 57, 66
metabolism 13, 28–9
  inhibition 29
metabolites 13, *29*, *29*–31
metergoline, interaction with LSD 123
methamphetamine, interaction with LSD 119, *127*
Methergine® 3
3-methoxytryptamine concentrations 98
D-L-methyl-2-bromine-LSD 19
methylandrostanolone, interaction with LSD 114, *126*
1-methyl-lysergic acid butanolamide (UML, methysergide, Deseril) 15, 17
  cross-tolerance with LSD *85*, 90
  distribution 23
1-methyl-lysergic acid diethylamide (MLD) 17
  cross-tolerance with LSD *85*, 90
methylphenidate (Ritalin), interaction with LSD 120, *121*, *127*
mice, distribution of LSD 21–3
micturition 58
military research ix, 6–7
Minnesota Paper Form Board Test performance, effect of LSD 145
MLD (1-methyl-lysergic acid diethylamide) 17
  cross-tolerance with LSD *85*, 90
model psychoses 4
molar mass 14
molecular structure *14*
monkeys
  excretion experiments 31
  plasma and cerebrospinal fluid LSD levels 25, *26*
  tolerance 83
monoamine oxidase inhibition 70–1
monoamine oxidase inhibitors, interaction with LSD 103, 104–5, 106
monosynaptic reflexes 59
mood changes 134
morphine, interaction with LSD 116, 117, *127*
Morris' Ways-to-live Test, effect of LSD 152
mutagenic effects 77–9
mydriasis 55, 59
mysticomimetic effects 135–6

nalorphine, interaction with LSD 117, *127*
natural killer cells, effect of LSD 72
neurological effects 59–60
neurons, effects of LSD 65
neuropsychological effects
  on abstract thinking 139–41
  on attention and concentration 137–9
  on estimation of weight, size and spatial relations 144–5
  on intellectual functions 141–2
  judgement of time 144
  on psycho- and visual-motoric abilities 143–4
neutrophilia 65, 66
nialamide, interaction with LSD 105, *124*

Bahan dengan hak cipta

nicotinamide, interaction with LSD 112
nicotinic acid, interaction
with LSD 112–13, *125*
nicotinic acid diethylamide (Coramin®) 3
NIMH (National Institute of Mental Health),
LSD research 11
NMDA (*N*-methyl-D-aspartate)-receptor-
induced neurotransmission,
effect of LSD 37
non-protein nitrogen levels 57
Nor1 expression 38
noradrenaline (norepinephrine) 48
and development of tolerance 86
interaction with LSD 94, 96, 97, 98
norbolethone, interaction with LSD 113
nor-LSD *29*, 30
nucleus accumbens 47
LSD binding 48
nucleus caudataus, LSD binding 48
nucleus reticularis 36, 40–1

oestradiol, interaction with LSD 113, *126*
oestrogen, interaction with LSD *126*
olfactory phenomena 131
onset of effects 13, 21
opiates, interaction with LSD 116–17, *127*
optical rotation 14
oral administration
lower threshold 51
pharmacokinetics 21
oxandrolone, interaction with LSD 114, *126*
oxidized LSD 19
2-oxo-3-hydroxy-LSD (O-H-LSD) *29*, 30
detection in urine 33
2-oxo-LSD *29*, 30
oxygen consumption, effect of LSD 66
1-oxymethyl-LSD 19

pain reflexes, loss of 59
para-bromo-methamphetamine,
cross-tolerance with LSD *85*, 90
parachlorophenylalanine, interaction with
LSD 123, *127*
paraesthesia-like sensations 131
paranoid thoughts 133
paroxetine, interaction with LSD *124*
patellar tendon reflex 59
pathological reactions, blood-relatives of
schizophrenics 149, *150*
peak of effects 13, 21
penicillamine, interaction with LSD 123, *128*
pentobarbital, interaction with LSD 115, *126*
pentolinium, interaction with LSD 118–19, *125*
perception, decoupling from conceptual
cognition 133
period-1 expression 38–9
perphenazine, interaction with LSD 100
personality disorders, effect of LSD 148–9
personality types, predisposition to adverse
reactions 154
perspiration 59
pH, optimal value for LSD metabolism 28
pharmacodynamics 33
effect on dopamine receptors 44–7
effect on serotonin receptors 33–44
potentiated effects 47–8
pharmacokinetics
distribution 21–6
excretion 31–2
metabolism 28–9
plasma levels 26–8
resorption 21
pharmacological effects 51
acute effects and toxicity 51–2
allergies, protective effect 71–2
analgesia 71
biochemical changes
alkaline phosphatase and acidic
phosphatase 71
carbohydrate metabolism 67–8
cholinesterase activity 69–71
fatty acids 69
phosphate metabolism 68–9
in blind subjects 64
on blood cells 65–6
body temperature 54–5
on brain cells 65
carcinogenic potential 72–3
cardiovascular 52–4
chromosomal damage 73–7
cross-tolerance 85–92
EEG studies 60–2
embryotoxicity
animal studies 77–8
human casuistics 78–9
on endocrine function and body
weight 57–8
on evoked potentials 62–4
on eyes 55–6
gastrointestinal 56–7
on immune system 72
on kidneys 58
neurological 59–60
on oxygen consumption 66
respiratory 54
on sleep-awake cycle and dream
experience 79–81
during sleep deprivation 81
summary 13, *52*
tolerance 81–2
neurochemical principles 84
tests on animals 82–3
tests on humans 83–4
phenelzine, interaction with LSD 105, *124*
phenethylamines, receptor affinities 47, 50
phenobarbital, interaction with LSD 116, *126*

Bahan dengan hak cipta

phenoxybenzamine, interaction with LSD 109–10, *125*
phentolamine, interaction with LSD *125*
Philadelphia chromosome 73
phosphate metabolism, effect of LSD 68–9
phosphatidyl inositol turnover 37
physical dependence 157
pizotifen, interaction with LSD 123
placental transfer, effect of LSD 74
placental transfer of LSD 77
plasma levels 26–7
plexus choroideus, LSD accumulation studies 24–5
Porteus Maze Test, effects of LSD *138*, 139
potency 15
potentiation of effects, interaction at different receptors 47–8
prednisone, interaction with LSD 114, *126*
pregnandiole, interaction with LSD *126*
pregnenolone, interaction with LSD *126*
pregnenolone-16 α-carbonitrile, interaction with LSD 114
progesterone, interaction with LSD 113, 115, *126*
prohibition of LSD *8*, 11
prolactin levels 58
prolonged adverse reactions *154*
promazine, interaction with LSD 102, *124*
pronethalol, interaction with LSD 109, *125*
propranolol, interaction with LSD 43, 109, *125*
proprioreception, effect of LSD 144
protease inhibitors, interaction with LSD 128
protein binding 13, 25–6
proverb interpretation, effect of LSD 140–1
pseudoesterase 70
pseudohallucinations 130
  in blind subjects 64
psilocybin 11, 20, 21, 87
  cross-tolerance with LSD *85*, 87–8
  effect on [^{11}K]-raclopride binding 46, 51
  effects on thalamus, FDG-PET studies 36
  5-HT$_2$ receptor affinity 50
  mystical experiences 135–6
  psychotherapeutic use 12
  research 12
'psychedelics', origin of term 9
psychedelic use of LSD 9–11
  psychedelic therapy 8, 136
psychiatric drugs, interactions with LSD
  antidepressants 103–6
  benzodiazepines 103
  chlorpromazine 99–102
psychoactivity, LSD derivatives 15–21
psychological dependence 157
psychological effects 129–30
  acoustic 130–1
  alterations of consciousness and ego functions 132–3
  changes in body perception 131–2
  changes in spatial and temporal perception 132
  changes to affectivity 133–4
  decoupling of perception and conceptual cognition 133
  hyperamnesias 135
  hypersuggestibility 132
  influencing factors *129*
  long-term 151–2
  mysticomimetic effects 135–6
  synaesthesias 132
  tactile 131
  thought disorders 132–3
  visual 130
psycholytic therapy 8
  see also psychotherapeutic use
psycho-motor abilities, effect of LSD *143*–4
psychophysical reactions, effect on catacholamine levels 98
psychotherapeutic use ix, 6, 7–9
  long-term effects 152–3
  methylphenidate as an adjuvant 120, *121*
  nicotinic acid as an adjuvant 112–13
  recent research 12
psychotic reactions 154
  incidence *153*
  treatment 102–3
pulse rate, effect of LSD 53
pupillary reflexes 59
pupil size 55–*6*, 59
Pursuit Rotor Test performance, effect of LSD *143*

Quick's hippuric acid test 56

[^{11}K]-raclopride binding, effect of psilocybin 46, 51
raphe nuclei 36, 40, 41, 43, 45, 48
  inhibition by antidepressants 104
  interaction of LSD and amphetamine 119
rats
  distribution of LSD 23–4
  excretion experiments 31
  tolerance 82
reaction times, effect of LSD *141*–2
receptor activation, time dependency 48, 51
receptor-binding
  dopamine receptors 44–7
  interactions
    potentiation of effects 47–8
receptors
  LSD affinity *49*
  synopsis of actions of LSD 48–51
  see also 5-HT receptors
religious experiences 135, 136
REM phase sleep, effect of LSD 80
renal effects 58

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research on LSD 1–2, 4, 4–5, 6
Cohen 9
long-term effects 153–5
military uses 6–7
psychotherapeutic use 7–9
restrictions 11–12
sciences involved 7
Stoll 3–4
summary 6
reserpine, interaction with LSD 106–8, *125*
resistance to LSD, schizophrenics 148
resorption 21
respiration, effect of LSD 53, 54
respiratory disturbance 51, 52
Restamin, interaction with LSD 122, 128
resurgence of use ix, 6
reverse transcriptase inhibitors, interaction with LSD 128
'reward system' of brain 47
Ritalin (methylphenidate), interaction with LSD 120, 121, 127
ritanserin, nullification of LSD effects 43
Rosenzweig-Picture-Frustrationstest, effect of LSD 152

'St Anthony's fire' 3
salivary flow, increased 59
Sandoz company
discovery of LSD 3–4
early distribution of LSD 4
SC 7294, interaction with LSD 115, *126*
SC 10592, interaction with LSD 115, *126*
schizophrenia
blood relatives, effect of LSD 149, *150*
comparison with LSD intoxication 5
effects of LSD 147–8
EEG changes 61
tolerance development 83–4
scopolamine, interaction with LSD 111, *125*
screening tests 32–3
seizures 62
effects of LSD in epilepsy 149–50
selective serotonin reuptake inhibitors (SSRIs), interaction with LSD 104, 105–6, *124*
self-control 134
seminal vesicles, effect of LSD 57
serotonin (5-hydroxytryptamine; 5HT) 48–50, 60
in anaphylactic reactions 71
interaction with LSD 93–*4*, 98
relationship to dreaming 80
serotonin receptors *see* 5-HT receptors
serotonin re-uptake inhibitors (SSRIs), interactions with LSD 44
sertraline, interaction with LSD 105–6, *124*
sex distribution, effect of LSD 79
sexuality, effects of LSD 131–2
sgk expression 38
Shagass, C. 63, 64
Shipley–Hartford Test, effect of LSD *141*, 142, 156
'signal-to-noise' relation, thalamus 40
size perception, effect of LSD 144, *145*
SKF 525-A, metabolism inhibition 28, 31
sleep–awake cycle, effect of LSD 79–81
sleep deprivation studies 81
Snapper–Saltzman test 56–7
sodium amytal, interaction with LSD 116, *126*
solubility 14
spatial perception, effect of LSD 132
spatial relations estimation, effect of LSD 144–*5*
speech comprehension, effect of LSD 141
spermatozoa production 77
spiritual experiences 10, 135–6
spironolactone, interaction with LSD 114, *126*
spleen, effect of LSD 57
stereoisomerism 14, 15
steroid levels, effect of LSD 58
steroids, interaction with LSD *126*
tests on animals 113–14
tests on humans 114–15
stillbirth 78
Strassman, R.J. 105
Adverse Reaction to Psychedelic Drugs 153–4
structure–activity relationships of LSD derivatives 15–21
structure of LSD molecule *14*
succinate, interaction with LSD 122, *128*
suggestibility 132
suicide attempts and suicide *153*
synaesthesias 132

tachistoscopic discrimination of circle size, effect of LSD *143*, 144
tactile phenomena 131
temporal perception, effect of LSD 132, 144
teratogenic potential
animal studies 77–8
human casuistics 78–9
terminally ill patients, LSD therapy 71
testosterone, interaction with LSD *126*
tetrabenazine, interaction with LSD 102, *124*
tetrahydrocannabinol (THC), cross -tolerance with LSD *85*, 91
thalamocortical loops 41, *42*
thalamus
action of hallucinogens 40–1, *42*
nucleus reticularis 36
therapeutic uses ix
see also psychotherapeutic use
thinking processes, effect of LSD 139–41, *140*
thought disorders 132–3
threshold dose 51

Bahan dengan hak cipta

effect of chlorpromazine 101
Thurstone Hand Test performance, effect of LSD *145*
thymus, effect of LSD 57
thyroid gland, effect of LSD 57
L-thyroxine, interaction with LSD 121, *127*
time dependency, receptor activation 48, 51
time judgement, effect of LSD 144
tolerance 81–2, 155
cross-tolerance 85–92
down-regulation of 5-HT_2 receptors 38
neurochemical principles 84
schizophrenics 148
tests on animals 82–3
tests on humans 83–4
toxicity 51–2
haemorrhage 66
trail-making A- and B-tests, effect of LSD use 156
transpersonal psychology 9
tranylcypromine, interaction with LSD 103, 105, *124*
triamcinolone, interaction with LSD 114
tricyclic antidepressants, interaction with LSD 106, *124*
triglyceride levels 69
tryptamine, cross-tolerance with LSD 91–2
tryptophan, interaction with LSD 95, *128*
L-tyrosine, interaction with LSD 121, *127*

UML (1-methyl-lysergic acid butanolamide) 15, 17
cross-tolerance with LSD *85*, 90
distribution 13
urinary excretion 28
urinary metabolites 30–1, 32–3
usage 1
uterus, effect of LSD 57

venlafaxine, interaction with LSD 104
visceral motor neurons, effect of LSD 36
visual effects 130
visual evoked potentials (VEPs), effect of LSD 62–4
'visualizers', effects of LSD 63
visual–motoric abilities, effect of LSD 143–4
vitamins, interaction with LSD 112–13, *125–6*
volume of distribution 24
vomiting 59
inhibition by LSD 117
VTA cells *42*

WAIS comprehension and information tests, effect of LSD use 156
Wechsler-Bellvue Test, effect of LSD 137, *138*, 140, *141*, 142
weight estimation, effect of LSD 144, *145*
Wisconsin Card Sorting Test, effect of LSD 140

zimelidin, interaction with LSD 44
zinc oxide (Restamin), interaction with LSD 122, *128*